IN THE UNITED STATES DISTRICT COURT FOR THE

SOUTHERN DISTRICT OF WEST VIRGINIA, HUNTINGTON DIVISION

BEFORE THE HONORABLE ROBERT C. CHAMBERS, JUDGE

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CLAUDE R. KNIGHT and CLAUDIA STEVENS, individually and as personal representatives of the Estate of BETTY ERLENE KNIGHT, deceased,

Plaintiffs,

vs. No. 3:15-CV-06424

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC., Volume 3
Pages 401 through 660

Defendant.
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REPORTER'S TRANSCRIPT OF PROCEEDINGS

JURY TRIAL

FRIDAY, OCTOBER 5, 2018, 9:00 A.M.

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For the Plaintiffs: CHILDERS, SCHLUETER & SMITH
1932 North Druid Hills Road, Ste 100
Atlanta, Georgia 30319
BY: C. ANDREW CHILDERS

URY & MOSKOW
883 Black Rock Turnpike
Fairfield, Connecticut 06825
BY: NEAL L. MOSKOW

(Appearances continued next page...)

Reported by: KATHY L. SWINHART, CSR
LISA A. COOK, RPR-RMR-CRR-FCRR
Official Court Reporters
(304) 528-2244

Proceedings reported by mechanical stenography, transcript produced by computer-aided transcription.

APPEARANCES (Continued)

For the Plaintiffs:

FERRER, POIROT & WANSBROUGH
2100 RiverEdge Parkway, Suite 1025
Atlanta, Georgia 30328
BY: RUSSELL ABNEY
and HUNTER VANCE LINVILLE

For the Defendant:

TUCKER ELLIS
925 Euclid Avenue, Suite 1150
Cleveland, Ohio 44115
BY: JOHN Q. LEWIS

COVINGTON & BURLING
One City Center
850 Tenth Street NW
Washington, D.C. 20001
BY: PHYLLIS ALENE JONES
and NICHOLAS HAILEY
and JESSICA PEREZ

JACKSON KELLY
Post Office Box 553
Charleston, West Virginia 25322
BY: GRETCHEN M. CALLAS

Also Present:

CLAUDE R. KNIGHT, Plaintiff

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HUNTINGTON, WEST VIRGINIA

FRIDAY, OCTOBER 5, 2018, 9:11 A.M.

THE COURT: All right. Are we ready to go?

MS. JONES: Your Honor, just one quick thing if I may. And I raised this with Mr. Moskow this morning.

As we discussed at the bench conference yesterday, we understand Your Honor's motion *in limine* ruling on this issue of whether experts can talk about motive or intent of the company, that that would be precluded.

My sense of Dr. Plunkett's testimony yesterday was that there were a couple of places where our view is that she probably crossed the line on that. There were references to the company twisting the science, for example.

We're not asking for any relief with respect to that testimony. But before we start cross-examination, before we have the redirect, I was going to ask if the Court would be willing either to let Mr. Moskow talk to her about the rules of the road or if Your Honor would give her some guidance outside of the presence of the jury, that would be helpful too.

THE COURT: Well, all right.

Mr. Moskow, do you want to respond?

MR. MOSKOW: Very briefly, Your Honor. I didn't hear it that way. But I am glad to talk to Dr. Plunkett and remind her of her obligation to stay within the lines of

your rulings.

THE COURT: Well, I think my ruling was that neither Dr. Plunkett nor other plaintiff experts could offer testimony where they purport to draw an inference from evidence and thereby form an opinion about the motivations of the company.

I didn't hear anything yesterday that I thought crossed the line. There were a number of times she quoted from the company. And the one instance you're talking about I do recall her testimony about, about that and I don't believe that crossed the line. But I certainly am happy for counsel to make sure that the witness understands.

MR. MOSKOW: Give me one moment, Your Honor.

THE COURT: Go ahead.

(Pause in proceedings)

MR. MOSKOW: All set, Your Honor.

THE COURT: All right. Let's bring the jury in.

(Jury returned into the courtroom at 9:13 a.m.)

MS. JONES: Thank you, Your Honor.

THE COURT: Good morning, ladies and gentlemen. We're ready to resume.

Dr. Plunkett, if you would return to the stand.

LAURA PLUNKETT, PLAINTIFFS' WITNESS, RESUMED THE WITNESS STAND

MS. JONES: May I proceed, Your Honor?

THE COURT: Yes.

BY MS. JONES:

Q. Good morning, Dr. Plunkett.

A. Good morning.

Q. And good morning, members of the jury.

Dr. Plunkett, when we finished our day yesterday, we were talking about the FDA's decision to approve a 75-milligram dose of Pradaxa for atrial fibrillation patients who have severe renal impairment. Do you recall that?

A. Yes.

Q. Okay. And I think I mentioned that I wanted to spend a little bit more time on that decision today when we have a little bit more of an opportunity to talk.

When we were going through that summary review document yesterday, do you recall that there were a listing of scientists and doctors at the FDA who had looked at the entire new drug application for Pradaxa; correct?

A. Yes.

Q. And some of those subject matter experts included people who were on a team known as the clinical pharmacology team. Do you recall that?

A. Yes.

Q. And do you recall from your review of the documents related to the FDA's consideration of the Pradaxa

application that the clinical pharmacology team actually generated a specific memo on the topic of their analysis of the application in that area?

A. Yes, I do.

MS. JONES: Your Honor, may I approach?

THE COURT: You may.

BY MS. JONES:

Q. Dr. Plunkett, I have marked -- I have handed you what we have marked for identification as Defense Exhibit 5813. Do you recognize that exhibit as the clinical pharmacology and biopharmaceutics review done by the clinical pharmacology team at the FDA on the Pradaxa application?

A. Yes, that's correct.

MS. JONES: Your Honor, we'd move for the admission of Exhibit 5813.

MR. MOSKOW: No objection.

THE COURT: It's admitted and may be published.

MS. JONES: Okay. Thank you, Your Honor.

(Exhibit 5813 admitted into evidence.)

BY MS. JONES:

Q. So just to orient ourselves, Dr. Plunkett, you see up at the top of that document, just like the summary review documents, there's a reference to the Center for Drug Evaluation and Research that analyzes applications for new medicines; correct?

A. Yes, that's correct.
Q. And you can see the title there, "Clinical pharmacology and biopharmaceutics review." Correct?
A. Yes.
Q. And you are, among other things, a pharmacologist; correct?
A. Yes.
Q. And so this is a memo that you would have paid attention to when you were going through the FDA materials in connection with your work in this case; correct?
A. Yes. It's often the first place I would go.
Q. We're going to go to the second page of Exhibit 5813. And, again, up at the top you see there's a reference to clinical pharmacology review; correct?
A. Yes.
Q. And then if you look down, there's a reference to the name of the product. Do you see that, brand name?
A. Yes.
Q. And that's, that's a reference to the medicine Pradaxa; correct?
A. Yes.
Q. And then if you go a little further down, there's a reference to something known as "Indication;" correct?
A. Yes.
Q. And "indication" just means this is what the medicine

is being proposed to be used for; right?
A. Yes.
Q. And what they have listed there is prevention of stroke and systemic embolism in patients with atrial fibrillation; correct?
A. Yes.
Q. And what that means is this is a medicine that's being proposed for treatment of patients with atrial fibrillation to prevent them from having a stroke caused by a blood clot traveling to the brain; correct?
A. Yes.
Q. Okay. And if we move a little further down, there are references to some of the reviewers on the application. Do you see that further down on the page?
A. I do.
Q. And so there's a listing of primary reviewers; correct?
A. Yes.
Q. And based on their titles there, you can see that there are PhDs and medical doctors who were involved; correct?
A. Yes.
Q. And then if you look a little further down, there are other reviewers who were part of that team. Do you see that?
A. Yes.
Q. So there's a pharmacometrics reviewer. There's a

genomics reviewer. And then there's a team leader. Do you see that?

A. Yes.

Q. And, again, just looking at the folks who evaluated the application with respect to clinical pharmacology, those are medical doctors. Those are folks who have PhDs like you do. There's someone here who has a PharmD degree; correct?

A. Yes.

Q. These are subject matter experts; correct?

A. Yes.

Q. If we look at the next page of Exhibit 5813, there's a Table of Contents. Do you see that?

A. I do.

Q. And that generally sets out the various different topics that this review memo covers in terms of reflecting what the clinical pharmacology team analyzed and determined based on their analysis of the Pradaxa application; correct?

A. Yes.

Q. And so at the top you see that there's an executive summary; right?

A. There is.

Q. And that includes recommendations by the clinical pharmacology team about what they thought the FDA should do with respect to Pradaxa; correct?

A. Yes.

Q. There's a section called "post-marketing requirements" where they're saying, "This is what we think the company, BI, should be required to do with respect to the medicine if it's approved." Correct?

A. After it's marketed, yes.

Q. Right, after it's marketed. Then there's a section called Phase IV commitments. And those are studies done after a clinical trial like RE-LY; correct?

A. Yes.

Q. All right. And then there's a section entitled "Summary of OCPD findings." And that just summarizes the different findings of the clinical pharmacology team based on its analysis; correct?

A. It is.

Q. Okay. And you can see just looking there that some of the things that they considered were things like pharmacokinetics, one of the topics you discussed yesterday; right?

A. Yes.

Q. They also considered things like exposure response relationships; correct?

A. They did.

Q. And that just means the relationship between how much of the medicine that you're getting and what types of events you might have in terms of bleeding or stroke; correct?

A. Not quite. It's how much actually gets into the blood in this case, not just how much your dose is. It's more than that as well. But I agree dose is part, but it's also -- they were also looking at the actual concentrations.

Q. And I think, I think we're on the same page. They were looking at how much of the medicine you're actually getting, not just the number on your dose; correct?

A. That's correct.

Q. Okay. So in terms of some of those curves that you showed the jury, those are the types of relationships that they were evaluating when they prepared this memo; correct?

A. That is correct, yes.

Q. All right. And then there's a section on drug-drug interaction information; correct?

A. There is.

Q. So the PhDs and the medical doctors at the FDA and the clinical pharmacology review team, they considered some of the issues that you discussed with respect to whether Pradaxa would interact with other types of drugs; correct?

A. Yes, based on the data they have, yes.

Q. Okay. And then there's a whole section that's devoted to question-based review. Do you see that?

A. I do.

Q. And I'm not going to go through all of those topics there. But basically what you see if you scroll down is

that the clinical pharmacology team at the FDA specifically looked at various types of questions that were relevant to their subject matter area related to the medicine; correct?

A. Yes.

Q. Okay. And then let's turn to the next page of this document if we could, Dr. Plunkett. There is a section entitled "List of Figures." Do you see that?

A. Yes.

Q. And so the clinical pharmacology team for Pradaxa at the FDA, they, they generated different figures based on their own independent analysis of the data that the company had submitted; correct?

A. I don't know that all of these are based on their independent analysis, but I agree that's mainly what is here.

Q. Okay. And then if we turn to the next --

Are we on Page 5, Mr. Reynolds? Down at the bottom. Thank you.

There's a section entitled "List of Tables." Do you see that?

A. Yes.

Q. And, again, that's just a description of some of the tables that are spread out throughout the contents of this memo reflecting some of the analysis by the clinical pharmacology team; correct?

A. Yes.
Q. Okay. If we turn to Page 7 of Exhibit 5813 there is a listing there of various members of the clinical pharmacology team at the bottom of the page. Do you see that?
A. Yes.
Q. And, again, those are just the doctors and the scientists, the PhDs, the PharmDs who actually looked at the data with respect to Pradaxa before its approval; correct?
A. Yes.
Q. And then if you turn to Page 8 of that same document, you see there's a section that begins with "CP briefing was held on August the 4th, 2010." Do you see that?
A. I do.
Q. And then there's a long listing of individuals who attended that briefing by the clinical pharmacology team in August of 2010. Do you see that?
A. Yes.
Q. And those are folks from various different parts of the FDA review team that actually looked at and worked on the application for Pradaxa; correct?
A. Yes.
Q. And so, for example, if you look at the second line of that list of names, there's a reference to Alison Blaus. Do you see that? That was the, the person inside the FDA who

was coordinating with the company. Do you recall that from your review of the documents?

A. I do, yes.

Q. Okay. And then if we look further down towards the bottom of that list, there's a reference to someone named Norman Stockbridge.

It's the fourth line up from the bottom, Mr. Reynolds.

Do you see that?

A. Yes.

Q. And Dr. Stockbridge is a senior person at the FDA who was involved in reviewing the application for Pradaxa; correct?

A. Yes. I believe he might have been the director of this division.

Q. Of the cardiorenal division?

A. That's correct.

Q. And so there were various folks in the clinical pharmacology review team who specifically looked at the data; correct?

A. Yes.

Q. And then there were people at the FDA beyond the clinical pharmacology team who were briefed by the clinical pharmacology team on what they found based on the data; correct?

A. That is correct.

Q. There was active discussion at the FDA concerning the application for this medicine; correct?
A. I wasn't there, but I would assume there was, yes.
Q. The documentation suggests that there was interaction at the FDA; correct?
A. That's correct.
Q. All right. Including with some of the most senior members of the cardiorenal division responsible for the application; correct?
A. Yes.
Q. Okay. I'm going to ask Mr. Reynolds to take us on the screen to Page 11 of this same clinical pharmacology review memo.

And this is a section, just to situate ourselves, if we go back to the prior page, the title is "Intrinsic Factors." Do you see that?
A. I do.
Q. And then there's a listing of different, what are essentially patient characteristics; correct?
A. Yes.
Q. Like body weight and like gender and like age; correct?
A. Yes.
Q. The FDA looked at all those different patient characteristics when they considered the application for Pradaxa; correct?

A. Yes.
Q. And then at the bottom of the page there is a reference to renal impairment. Do you see that?
A. Yes.
Q. And the first sentence in that bullet says, "Exposure to dabigatran increases with the severity of renal function impairment as demonstrated in the dedicated renal impairment study."
Did I read that correctly?
A. You did.
Q. And that's a true statement; correct?
A. That is true.
Q. The FDA was fully aware that exposure to Pradaxa would increase in patients as their kidney function got worse; correct?
A. Yes.
Q. And then if you turn to the next page in that same document, there is a second bullet. Do you see that, Dr. Plunkett?
A. I do.
Q. It says, "At the mid --" I added "the." "At mid-cycle meeting the review team expressed the need to propose a dosing regimen in severe renal impaired subjects for the current indicated population."
Did I read that correctly?

A. You did.
Q. And that reference to a mid-cycle meeting and the review team, do you understand that to be a meeting that involved folks at the FDA who were responsible for reviewing the application for Pradaxa?
A. Yes.
Q. And just to understand the history here, do you also understand that to reference the fact that during one of those meetings that the folks at the FDA had, there were, there were members of the team who said, "We need to have a dose option for Pradaxa for patients with severe renal impairment"?
A. Again, I wasn't there but certainly, yes, I'm aware of there was discussion about that.
Q. And that's what the document says; correct?
A. That is correct.
Q. All right. And when it says "for the current indicated population," they're talking about for the atrial fibrillation population; correct?
A. Yes, that's correct.
Q. And the next few sentences cover some of the topics that we've already talked about yesterday in terms of figuring out what the dose would be for those patients. But I actually wanted to focus on the last sentence in that same bullet point section. Do you see that sentence that starts

with, "It should"?

A. Yes.

Q. It says, "It should be noted that there is no efficacy or safety information available at the proposed dosing regimen of 75 milligrams dabigatran once a day," or QD, "in severe renal impairment."

That's what it says; correct?

A. It does, yes.

Q. And just to be clear on one thing, when the discussions regarding having a dose for severe renal impairment patients started, it looks like, based on the documents, that they initially considered a 75-milligram dose of Pradaxa once a day as opposed to twice a day. Is that right?

A. They did.

Q. That was one of the options they considered; correct?

A. Yes. I think we looked yesterday at their different modeling for different things.

Q. Exactly, okay. And this memo reflects that the FDA fully understood there was no data for the 75-milligram dose of Pradaxa that would be available for patients with severe renal impairment; correct?

A. Yes. The agency certainly understood that.

Q. I'm going to ask you to go back to Page 6 of that same document, Exhibit 5813. And there's a section entitled "Recommendations." Do you see that?

A. On Page 6? Yes.
Q. Page 6, yes. And just to frame this section, it says, "The office of clinical pharmacology has reviewed the clinical pharmacology and biopharmaceutics information submitted to NDA 22-512."
Did I read that correctly?
A. You did, yes.
Q. And that's just a reference -- that number is just a reference to the number that was assigned to the new drug application for Pradaxa and atrial fibrillation; correct?
A. Yes, that's the number.
Q. It goes on to say, "The CPB information provided in NDA 22-512 is acceptable following agreement with sponsor regarding specific labeling language and post-marketing requirements. The office has the following specific recommendation." Do you see that?
A. I do.
Q. And then there are a series of bullets that reflect the recommendations of the doctors and the scientists within the Office of Clinical Pharmacology who had reviewed the data submitted to the agency; correct?
A. Yes.
Q. And the second recommendation there is, "Patients with severe renal impairment should receive 75 milligrams once a day." Correct?

A. Yes.
Q. That was their recommendation even in light of their acknowledgment that there hadn't been data collected from the RE-LY study for patients who might have been on a 75-milligram dose; correct?
A. Yes, that's correct.
Q. If we go to the next page, which is Page 7 of 5813, there's a section -- I want to actually look at both the sections entitled "Post-marketing requirements and Phase IV commitments." Do you see that?
A. Yes.
Q. And the clinical pharmacology team at the FDA included as a post-marketing requirement for Boehringer Ingelheim the following:
"The sponsor should manufacture a lower strength of 75-milligram and demonstrate bioequivalence following the administration of two times 75-milligram versus 150 milligrams for BIBR 1048 MS." Do you see that?
A. Yes.
Q. And without getting into all of the technical language there, that's just informing the folks who were reviewing this memo that the clinical pharmacology team, having reviewed all of that data, determined that BI needed to manufacture what was essentially a half dose of Pradaxa 150 for patients who had severe renal impairment; correct?

A. Yes. That -- well, say that again. I'm sorry. Are you saying a half dose of 150 or a lower strength of 75? I think they're talking about --

Q. Well, should -- I think when they say a lower strength of 75, they're referring to the need for the company to have available a 75-milligram dose of the medicine; correct?

A. Yes, I agree. That's true.

Q. Okay. And then it goes on to say, "This strength will allow for the dose adjustment in severe renal impaired patients." Correct?

A. That's what they state, yes.

Q. Okay. And then there's another section that's entitled "Phase IV commitments." Do you see that?

A. Yes.

Q. And that's a place where the agency has the ability to say, "We think in addition to whatever study the company has already done, here are some additional things that they should do in further studies." Correct?

A. Yes.

Q. Okay. And this talks generally about the need for doing what are known as in vitro studies involving two medicines, Amiodarone and Dronedarone. Do you see that?

A. Yes.

Q. Okay. That was their recommendation in terms of Phase IV commitments; correct?

A. Yes.
Q. Now, after the approval of Pradaxa, some of the members of that same clinical pharmacology team actually published a paper in a journal discussing the FDA's analysis of the 75-milligram dose; correct?
A. They did.
MS. JONES: May I approach, Your Honor?
THE COURT: Yes.
BY MS. JONES:
Q. Dr. Plunkett, I have handed you what has been marked for identification as Defense Exhibit 6038. Do you recognize Exhibit 6038?
A. I do.
Q. Okay. And do you recognize it as an article that was published by two members of the clinical pharmacology team at the FDA on the subject of the FDA's decision to create a 75-milligram dose for patients with severe renal impairment?
A. Yes, that's true.
MS. JONES: Your Honor, we'd move for the admission of Exhibit 6038.
MR. MOSKOW: My understanding is it's being used as a demonstrative, not as a full exhibit, and we have no objection to that.
MS. JONES: In connection with our discussion in the conference room.

THE COURT: You may proceed.

MS. JONES: Thank you, Your Honor.

BY MS. JONES:

Q. Dr. Plunkett, again just to situate ourselves, up at the top of the page you see there's a title there, "Clinical pharmacology basis of deriving dosing recommendations for dabigatran in patients with severe renal impairment." Do you see that?

A. I do.

Q. And that's a, that's a way of saying this is how the clinical pharmacology team came up with a dose recommendation for Pradaxa patients who have severe renal impairment; correct?

A. Yes, with the caveat they say in here that this is not the official position of the FDA. It's the author's position. But I agree with you this is consistent with what we just saw.

Q. Okay. But the, the subject matter of this article doesn't deviate or significantly differ from what some of the, some of the things you've already discussed with regard to the review memos; correct?

A. Yes, with the exception of there are opinions expressed by these two gentlemen in here. And that's why they have -- one of them may be a woman. But this, this is their opinions. And, so, they have a caveat at the end where they

say this is not an official statement by the FDA.
Q. Understood.
A. Yeah.
Q. Let me just ask you this question since you've raised that point. Is there anything in this article that you've seen, having had a chance to review it, that you think somehow contradicts or diverges from the analysis you've seen by the FDA on this subject in the review memos?
A. No. There's additional information here that isn't presented in the review memos. But that's, that's why I'm making that caveat. It's not like this is -- they took this and published the review memo. It is, it is a little different than that.
Q. Understood. There is an identification of the two scientists who were authors on those papers, Dr. Hariharan and Dr. Madabushi. Do you see that?
A. Yes.
Q. And if you look down in the bottom left-hand corner of the paper, there is a reference to what their affiliation is, where they work. Do you see that?
A. Yes.
Q. It says, "From the Office of Clinical Pharmacology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration." Do you see that?
A. I do.

Q. Okay. If we just -- I don't -- we don't have to go through every single word of this. But just to look at the, the incomplete paragraph on the right-hand side, do you see there's a sentence that says, "This report is aimed at" -- we're going to call it up on the screen as well.

"This report is aimed at providing the clinical pharmacology basis for the recommendation of dabigatran 75-milligram in patients with severe renal impairment." Correct?

A. That's what it says, yes.

Q. And that's what we were talking about in terms of just the title for the paper; correct?

A. Yes.

Q. They're, they're explaining their thinking on that.

If we go to the next page of that same article, there is a full paragraph there that, that starts with the sentence, "The role of renal function." Do you see that? We'll call it up again on the screen.

A. Yes. It helps if you --

Q. Yes, understood.

A. I see it now.

Q. And that sentence reads, "The role of renal function is evident from the results of a dedicated renal impairment study that evaluated the pharmacokinetics of dabigatran 150-milligram after a single oral dose in healthy subjects

and those with renal impairment."

And then it goes on to define what those different levels of renal impairment were.

And do you understand that to be a reference to I think the Phase I study that you were describing yesterday?

A. Yes.

Q. Okay. And then about midway through that paragraph there is a sentence that begins with, "Patients with severe renal impairment." Do you see that?

A. I do.

Q. And it specifically says, "Patients with severe renal impairment are inherently at a higher risk for stroke and bleeds. They are most often not enrolled in cardiovascular trials, as so in RE-LY." Do you see that?

A. I do.

Q. And do you agree that that statement is correct that patients with severe renal impairment are inherently at a higher risk for stroke and for bleeds?

A. Yes. I'm aware of that data.

Q. Okay. Is it also true, as these two authors from the FDA report, that these patients are most often not enrolled in cardiovascular trials as so in RE-LY? Is that a true statement?

A. Yes. I think we discussed that yesterday. But, yes, I agree with that.

Q. And so it's not an unusual thing necessarily that patients who have severe renal impairment might not be part of one of the large types of clinical trials that you were describing yesterday like the RE-LY study; correct?

A. Yes, that's true.

Q. Towards the bottom of that paragraph it goes on to say, "Therefore, due to a lack of clinical experience, Boehringer Ingelheim Pharmaceuticals, Inc., saw contradiction in patients with severe renal impairment on hemodialysis --" "and on hemodialysis."

Did I read that correctly with that correction?

A. You did.

Q. And so that's just a reference to the fact that initially when the company submitted an application for Pradaxa, it said, "We don't think that patients who have severe renal impairment would be receiving Pradaxa because we didn't test those patients in the last study." Correct?

A. Yes.

Q. It goes on to say that, "Given the lack of treatment options for patients with severe renal impairment, during the review of dabigatran new drug application, NDA 22-512, the FDA explored the possibility of deriving dosing recommendations for this population." Correct?

A. That's what is stated, yes.

Q. Right. So that's just that chronology we talked about

yesterday. The company made a proposal with regard to severe renal impairment and the FDA reached a conclusion that given the lack of options for patients with severe renal impairment, there should be a dose of Pradaxa available for patients; correct?

A. Yes, that's true.

Q. Let's go to the next page of this paper. There's a section entitled "Discussion" on the left-hand side. We'll pull that up for you.

At the very top of that "Discussion" section, it says, "Incidence of AF in patients with CKD is high." Do you see that?

A. I do.

Q. And just to define those acronyms, AF is a reference to atrial fibrillation; correct?

A. Yes.

Q. And CKD is a reference to chronic kidney disease; correct?

A. Yes.

Q. And "incidence" means what?

A. How often it occurs.

Q. Okay. And so what that sentence is telling us is that AF occurs often in patients who have chronic kidney disease; correct?

A. Yes.

Q. Later on in that paragraph it says, "Importantly, incidence of stroke, which is a major complication of AF, increases significantly with worsening of renal function." Correct?

A. You read that correctly, yes.

Q. And that's a true statement; correct?

A. Yes. Based on data I've seen, that would be true.

Q. And that just means that when patients have poor renal function and their renal function continues to decline, their chances of having a stroke increase; correct?

A. Yes. In other words, those two things go together based on some of the data that's available.

Q. Okay. In that same paragraph these two FDA scientists write, "Moreover, the two-year mortality rates after occurrence of a stroke or transient ischemic attack also increase dramatically in patients with CKD and hemodialysis as compared to those without CKD."

Did I read that correctly?

A. You did.

Q. And just to again define some of the terms here, two-year mortality rate refers to the, the number of people who have passed away after they've had either a stroke or what's sometimes referred to as a mini stroke, a transient ischemic attack; correct?

A. The first part of the sentence, yes, that's what

they're talking about.
Q. Okay. And that rate, according to these FDA authors, actually increases dramatically when patients have chronic kidney disease; correct?
A. That's what they state, yes. Well, they don't give a number to show how much of those -- well, that's fine. They give a number for going up.
Q. And they're comparing those patients against patients who don't have chronic kidney disease; correct?
A. That's correct, yes.
Q. Okay. The next statement that the FDA authors make based on that data that they referenced is that, "AF patients with renal insufficiency are in utmost medical need for an appropriate anticoagulant treatment."
Did I read that correctly?
A. You did.
Q. And that means that patients who have atrial fibrillation and also have problems with their kidneys are at a particular need for a good anticoagulant medicine; correct?
A. For an appropriate anticoagulant medicine, that is true.
Q. Okay. Now, it goes on to say later in that same paragraph starting with "moreover," "Moreover, to decrease the noise and avoid misinterpretation of primary efficacy

and safety results, a majority of the cardiovascular trials do not enroll patients with severe renal impairment because of higher background rates for both stroke and bleeds."

Did I read that correctly?

A. You did.

Q. And what the FDA scientists are saying there is the point that we talking about earlier; that it's commonly the case that patients with severe renal impairment are not included in trials for medicines addressing cardiovascular issues because those folks have other problems that might complicate the interpretation of the data. That's that reference there to noise and misinterpretation of primary efficacy and safety results. Correct?

A. Yes, but it's a little more complex than that. Do you want me to explain or --

Q. Why don't I, why don't I move on to my next question.

A. Okay. That's fine.

Q. But we can agree that this is just -- it's an echoing of the point that we talked about earlier; that a majority of clinical trials for medicines that are intended for patients with cardiovascular issues, heart issues don't include patients who have severe renal impairment; correct?

A. That I agree with, yes. I think there's other reasons, though, that aren't described here. But I would agree with that.

Q. Okay. Understood. And, so, just to ask the question, that, that can sometimes create a challenge because patients who have severe renal impairment could also have cardiovascular illness that needs to be treated; correct?

A. Yes. They can be complex patients.

Q. Okay. And so what, what we see in some of the documentation relating to Pradaxa in particular is a discussion about identifying a dose with respect to Pradaxa that would be available for patients who have severe renal impairment but also need protection from stroke because they have atrial fibrillation; correct?

A. That's what FDA is discussing. I would agree.

Q. Okay. The next sentence on this same point says, "Therefore, any clinical experience to treat this important subgroup of patients is very scarce." Do you see that?

A. Yes.

Q. And that just means for patients who have severe renal impairment, this important subgroup of patients, it is not unusual that you wouldn't have clinical trial data to be able to support an application for cardiovascular medicine; correct?

A. Yes, because they're not typically included. That's, that's the main issue.

Q. Okay. Further down that same page there is a reference in the next column to dose adjustment for special

populations. Do you see that?
A. I do.
Q. And let me just ask you, do you agree with the statement that we read earlier that any clinical experience to treat the important subgroup of patients known as severe renal impairment patients, that is scarce? Is that a true statement as far as you're concerned?
A. It is, it is definitely generally because of the issue of, of them not being in the trial. So that's the issue.
Q. Okay. And then further down in that column it says, "Dose adjustment for special populations can be derived using pharmacokinetic approaches as stated in the guidance for industry pharmacokinetics in patients with impaired renal function, study design, data analysis and impacts on dosing and labeling." Do you see that?
A. Yes.
Q. And, and all that's referring to is the FDA's view that figuring out doses for special populations like severe renal impairment patients, that can be achieved using pharmacokinetic approaches like modeling; correct?
A. Yes, but the guidance gives specific recommendations for when it's appropriate and when it's not.
Q. Okay. Do you agree with just that statement in this article by these FDA authors that dose adjustment for special populations can be derived using pharmacokinetic

approaches?

A. Certainly you can do it. The question is in all cases should you do it. But absolutely it can be done.

Q. Okay. And just to go back to a discussion that we were having earlier yesterday, do you have a view on whether the FDA was, was wrong or incorrect in deciding with respect to Pradaxa that it would use pharmacokinetic modeling to identify a dose for patients with severe renal impairment?

A. No. And I think I answered that yesterday. I have not formed that opinion that they were wrong.

Q. Okay. We're going to turn to Page 6 of the same document moving toward the conclusion. There is a discussion that starts on the left-hand side of the article and then carries over to that right-hand side column.

And at the very top of that top not complete paragraph there's a sentence that says, "Only the dabigatran 75-milligram BID regimen provided a reasonable alternative with respect to matching exposures." Do you see that?

A. I do.

Q. And I didn't want to walk us back through all the discussion that we had yesterday, but that's essentially the FDA concluding after having gone through the different dose options that it considered that the 75-milligram twice a day dose would be the best option for patients who have severe renal impairment; correct?

A. In the other document I agree that they concluded that. And that is a different paper. But certainly this is consistent with the document we looked at yesterday, yes.

Q. Okay. Those two things are not -- they didn't reach a different conclusion in this paper than what we saw in the review memo; correct?

A. That is true.

Q. Okay. And then at the end of that paragraph it says, "Furthermore, from a practical viewpoint the 75-milligram BID regimen in severe renal impairment provides an option that is easy to implement with reduced potential for prescription errors." Do you see that?

A. Yes, I do.

Q. Do you agree or disagree with that statement by these two FDA authors?

A. I haven't formed an opinion on this one way or the other.

Q. Okay. Let's move on to the conclusion. There's, there's a statement at the very beginning of the concluding paragraph in that paper that says, "Conducting safety and efficacy trials that adequately represent all categories of renal function is a challenge."

Did I read that correctly?

A. You did.

Q. Is that a true statement?

A. Yes.
Q. It goes on to say, "Depending on the data from large Phase III trials the deriving dosing recommendation --" let me start that one over again. "Depending on the data from large Phase III trials for deriving dosing recommendations in special populations is not always practical."
Did I read that correctly?
A. Yes.
Q. Okay. Do you agree with that statement?
A. I think that is dependent on the trial. But certainly in some trials it may be, yes, depending on how many patients or what the drug is going to be used in, what population. But I'd say that's possible, yes.
Q. Okay. It goes on to say, "Quantitative clinical pharmacology approaches can provide a powerful alternative to derive meaningful dosing recommendations for special populations."
Did I read that correctly?
A. You did.
Q. Do you agree or disagree with that statement by these two FDA authors?
A. I agree in part and disagree in part. Would you like me to explain?
Q. Which part do you -- just tell me which part you disagree with first.

A. I agree that it can be an alternative. But there's particular considerations you have to do when you talk about the study itself. Do you want me -- that's what I wanted -- do you want me to explain that?

Q. Well, is there a portion of that statement that you specifically disagree with or are there just nuances you would add to what they've written here?

A. It's not just a nuance. I think there's an important, there's an important thing you have to understand in order to say, yes, I agree with that or I don't agree with that. I think they're missing a concept.

Q. Okay, fair enough. Let's move on in this concluding paragraph. "The analysis presented in this article illustrates the use of a simple pharmacokinetic modeling and simulation approach to derive dosing recommendations for patients with severe renal impairment based on the results of dedicated renal impairment study and the understanding of safety and efficacy across renal function categories from the pivotal registration trial." Do you see that?

A. Yes.

Q. And what they're essentially saying there is the analysis that they've outlined in this article shows the use of pharmacokinetic modeling based on some of the data that was collected during the Pradaxa study period to come up with a dosing approach for patients who have severe renal

impairment. Correct?
A. That's what they're trying to say, yes.
Q. Okay. And recognizing that you may not fully agree with the statement, do you have any reason to think that this statement that quantitative clinical pharmacology approaches can provide a powerful alternative to derive meaningful dosing recommendations for special populations, do you have any reason to believe that that's somehow inconsistent with the views of the broader clinical pharmacology team that reviewed the application for Pradaxa?
A. I haven't spoken to them. But based on general principles of clinical pharmacology, do you want me to speak to it that way? I haven't spoken to the team, so I -- and that's what I think you're asking me. But --
Q. You, you've reviewed the memorandum prepared by the clinical pharmacology team related to the Pradaxa application; correct?
A. Yes, I have.
Q. And you've had an opportunity to review various other materials generated by members of the Pradaxa review team at the FDA; correct?
A. Yes, I have.
Q. Have you seen anything in any of those written materials that you view as being inconsistent with this statement that quantitative clinical pharmacology approaches

can provide a powerful alternative to derive meaningful dosing recommendations for special populations?

A. Yes.

Q. You have seen something that's inconsistent with that?

A. Yes.

Q. Okay. In the clinical pharmacology review?

A. In the, in the discussion of the data that they use for the review, yes, and in this paper too if you want me to show you. But --

Q. Well, I want to finish this paragraph because I want to be efficient with your time and with the jury's time.

Just to round out our discussion of the conclusion, it says, "Based on our analysis, dosing recommendations for patients with severe renal impairment were incorporated in the U.S. prescribing information for dabigatran." Do you see that?

A. I do.

Q. And that just means based upon the analysis of the clinical pharmacology team at the FDA, there was a dose that was recommended for patients who have severe renal impairment; correct?

A. Yes. That's the ultimate outcome. That's true.

Q. Now, you're, you're familiar with --

We can take that down. Thank you, Mr. Reynolds.

You're familiar with the medicine known as Xarelto;

correct?
A. I am, yes.
Q. You're actually involved as a litigation expert in cases against the makers of that medicine as well; correct?
A. I am.
Q. All right. And are you aware that the, the lower dose for Xarelto for patients with severe renal impairment was approved without any safety or efficacy data from the Phase III trial for the medicine?
A. Yes, I am.
Q. Now, in addition to the modeling that the FDA had done for the Pradaxa 75-milligram dose for severe renal impairment patients, the company, BI, actually conducted and published its own pharmacokinetic modeling regarding the 75-milligram dose; correct?
A. They did.
MS. JONES: May I approach, Your Honor?
THE COURT: You may.
BY MS. JONES:
Q. Dr. Plunkett, I've handed you what is marked as Exhibit 3199. Do you see that number at the bottom?
A. I do.
Q. Okay. And do you recognize that as an article that was published by various authors at Boehringer Ingelheim on the subject of modeling related to the 75-milligram dose of

Pradaxa?

A. Yes, that's correct.

Q. Okay. And we've, we've talked about this issue at some length so I'm just going to go through it relatively quickly. If we turn to --

And I apologize, Your Honor. We would move for the admission of 3199, please.

MR. MOSKOW: As a demonstrative, no objection.

THE COURT: All right. You may use it in your examination of the witness.

MS. JONES: Thank you, Your Honor.

BY MS. JONES:

Q. And again, Doctor, just to situate ourselves, do you see there's a title there "Dabigatran etexilate in atrial fibrillation patients with severe renal impairment?" Do you see that?

A. Yes.

Q. And that's just a reference to Pradaxa in patients who have atrial fibrillation and also have very severe kidney problems; correct?

A. Yes.

Q. Okay. And then the subtitle is "Dose identification using pharmacokinetic modeling and simulation." Correct?

A. Yes.

Q. And that just means finding a dose for these patients

who have AFib and also have severe renal impairment using pharmacokinetic modeling; correct?

A. Yes.

Q. All right. And then the authors on this paper are folks who were employed by Boehringer Ingelheim; correct?

A. Yes, all of these are.

Q. Okay. And this was a paper that was published in something known as the *Journal of Clinical Pharmacology*. Is that right?

A. Yes.

Q. All right. If we turn to the second page of that paper, I just very quickly want to talk about some of the introductory information. There's a paragraph that begins with, "Atrial fibrillation patients with severe renal impairment." Do you see that?

A. I do.

Q. It reads, "Atrial fibrillation patients with severe renal impairment are known to be at higher risk of stroke than patients with preserved renal function." Do you see that?

A. Yes.

Q. And that's that same concept that we were talking about earlier, that patients who have atrial fibrillation and also have severe renal impairment are at a higher risk of stroke than patients who have better renal function; correct?

A. Yes. I agree it's the same type of statement we saw in the first page.

Q. Okay. And then at the bottom of that paragraph it describes the purpose of the analysis reflected in this paper. "The aim of this analysis was to derive such a dose and dose regimen for AF patients with severe renal failure who could potentially benefit from the use of DE." Do you see that?

A. Yes.

Q. And do you understand that reference there to DE to be a reference to Pradaxa, dabigatran etexilate?

A. Yes. It's an abbreviation for essentially the same compound.

Q. Okay. And so what the, what the authors of this paper are explaining is the purpose of the analysis that's described here is to outline how using pharmacokinetic modeling you might come up with a dose for patients who have severe renal impairment; correct?

A. Yes.

Q. And then if you look down under the "method" section there's a reference at the very beginning of that section to simulation purposes. Do you see that?

A. Yes.

Q. It says, "For simulation purposes the final population PK model based on data from 9,522 patients from the pivotal

Phase III study (RE-LY) was applied." Do you see that?
A. I do.
Q. And then it goes on to talk about how the company developed a different model than the one that the FDA had actually used for its approval decision and how they used that model to try to identify an appropriate dose; correct?
A. Yes.
Q. If we go to Page 5 of that same document, please, there is a section called "Discussion." Do you see that?
A. I do.
Q. And the second sentence of that section called "Discussion," says, "Since renal clearance is the predominant excretion pathway of dabigatran, the impact of renal function on exposure was investigated during DE development." Do you see that?
A. Yes.
Q. And that's just another way of saying because the way Pradaxa is excreted through the body is through the kidneys, there was a particular -- there was an interest in looking at the impact of renal function on exposure or blood levels while the medicine was being investigated; correct?
A. Yes.
Q. Okay. If we look down on the next column there, there is a section entitled "Conclusion." Do you see that?
A. Yes.

Q. And then the third sentence in that conclusion explains that, "Based on simulated exposure data using a model based on data from the actual RE-LY trial, AF patients with creatinine clearance less than 30 but higher than 15 treated with a dabigatran dose of 75 milligrams twice a day have target plasma level and exposure data largely within the concentration range proven to be safe and effective in AF patients with creatinine clearance that was greater than 30 milliliters per minute receiving 150 milligrams of Pradaxa twice a day." Do you see that?

A. Yes.

Q. And it goes on to say, "Through interaction with the FDA, this dosing algorithm was also confirmed and supported by the FDA clinical pharmacology division using their model based on the data from the dedicated renal impairment study taking into account the safety and efficacy information from RE-LY." Do you see that?

A. I do.

Q. And so what they're saying there is the FDA developed a model based on data from that Phase I study involving renally impaired patients that you talked about yesterday; correct?

A. Yes.

Q. And that model was the basis of the FDA's decision to actually approve the 75-milligram dose twice a day for

patients with severe renal impairment; correct?
A. Yes.
Q. At the same time, the company did its own models that included data from patients in the RE-LY study; correct?
A. Yeah. It was a different, different modeling exercise, but, yes, they did.
Q. They did a different model; correct?
A. Yes.
Q. And what they say here is at the end of this paragraph, "These results support the use of dabigatran 75 milligrams twice a day in AF patients at risk of stroke and with creatinine clearance values between 15 and 30 milliliters per minute." Did I read that correctly?
A. You did.
Q. Okay. And so what happened was the FDA created its own model using that Phase I data that you described yesterday; correct?
A. Yes.
Q. And based on that model, the FDA reached a conclusion that the 75-milligram twice-a-day dose was the appropriate dose for patients with severe renal impairment; correct?
A. That was what they based -- that's what they point to as the basis for their decision, yes.
Q. Okay. And then the company created a model, used a different approach, but also did a modeling exercise to

evaluate the same question of dosing in patients with severe renal impairment; correct?

A. Yes.

Q. And they ultimately concluded that the results of their modeling exercise also supported the use of Pradaxa 75 milligrams twice a day in atrial fibrillation patients at risk of stroke and with severe renal impairment; correct?

A. I disagree.

Q. You disagree that the company came to that conclusion?

A. Yes, based on other documents I have seen.

Q. Okay. Well, I want to just focus on the document we're looking at at the moment. That sentence that we just read, "These results support the use of dabigatran 75 milligrams twice a day in AF patients at risk of stroke and with creatinine clearance values between 15 and 30 milliliters per minute."

That's what that's saying; right? We did our models and we think the results support the same dose that the FDA recommended; correct?

A. I don't disagree the statement is here. I disagree that that's the company's position based on other things I have seen.

Q. Okay. Well, I'm just asking you about the statement we're looking at right now.

A. I agree that statement is here, absolutely.

Q. Okay. And then the modeling that, that Boehringer Ingelheim did that's described in this paper that we just went through, that, that data was submitted to the FDA; correct?

A. Yes.

Q. Now, are you aware, based on your review of the documents in the case, that after Pradaxa was approved that the company conducted small, additional studies regarding the use of the 75-milligram dose in patients with severe renal impairment?

A. I think I -- well, I need to see what you're referring to. I'm aware there was some things done, yes.

Q. Okay.

MS. JONES: May I approach, Your Honor?

THE COURT: You may.

BY MS. JONES:

Q. Dr. Plunkett, I've handed you what we've marked for identification as Defense Exhibit 9194. Do you recognize that exhibit?

A. I'm not sure I've seen this exact exhibit, so let me look for a second --

Q. Okay.

A. -- to see what the, the -- I don't know if I've seen it in this form, no, I can't tell you that. But we can talk about it. I'm, I'm --

Q. You're happy to talk about it?
A. Yeah, because I know what -- I mean, I understand what's in here.
Q. Okay.
MS. JONES: Your Honor, given that, we would move for the admission of Exhibit 9194.
MR. MOSKOW: No objection.
THE COURT: It's admitted and may be published.
(Exhibit 9194 admitted into evidence.)
MS. JONES: Thank you, Your Honor.
BY MS. JONES:
Q. So, Dr. Plunkett, just to situate ourselves up on the screen, do you recognize this as a clinical trial report for a trial done by BI that had the number 1160.166?
MR. MOSKOW: Excuse me, counsel. Could I talk to you one second?
MS. JONES: Yes, of course.
(Ms. Jones and Mr. Moskow conferred off the record, after which the following occurred:)
MR. MOSKOW: Thank you, Your Honor.
BY MS. JONES:
Q. And, Dr. Plunkett, just in the interest of fairness, as Mr. Moskow rightly points out, I just want to note that this is Page 1 of 390. If you, if you need to see the remaining 300 or so pages, we're happy to get those for you. But I'm

probably going to ask you a few questions. If you need more, just let us know. All right?

A. All right, sure.

Q. And just moving down in that same section at the top of that clinical trial report, the title reads "An exploratory study to investigate the pharmacokinetics and effects of dabigatran etexilate in patients with stable severe renal disease." Do you see that?

A. Yes.

Q. And then it says "dabirenal." Do you see that?

A. Yes.

Q. Are you familiar with, having looked at some of the documents, to something that's known as the dabirenal study that the company did?

A. I -- again, I'm not sure I've seen this quite this way. That's my problem. And I don't think this is an atrial fib study, but maybe I'm wrong. I would need to see the report to confirm that.

Q. Okay. If you look further down on that same page, you see the date of the report is September the 19th, 2014.

A. Yes, that's true.

Q. Do you see that? And then it actually identifies the dates of the trial as starting in January, 2013 and ending in December of 2013. Do you see that?

A. I do.

Q. Okay. And then if we go to Page 3 of that same document, there's various information here just regarding some of the details of the study. You see there's a reference there to the name of the finished product which is Pradaxa up in the upper left-hand corner. Do you see that?
A. Yes.
Q. And then if you scroll further down, there is a section that refers to the title of the trial. Do you see that?
A. Yes.
Q. And that's just the title we looked at earlier; correct?
A. Yes.
Q. And then there's a section entitled "Objectives." Do you see that?
A. Yes.
Q. And it says, "The objective of this trial was to evaluate the pharmacokinetics and pharmacodynamics of dabigatran etexilate in patients with severe chronic kidney disease, CKD, as defined by creatinine clearance between 15 and 30 milliliters per minute over the last three months before study participation." Do you see that?
A. Yes.
Q. And then it goes on to say -- describes the methodology. Do you see that?
A. I do.

Q. And then there's a section that refers to the fact that there were a certain number of subjects. Do you see that?
A. Yes.
Q. And that -- it was a small study; correct?
A. Yes.
Q. If you turn to Page 7 of the document, do you see that there's a reference to conclusions? Does your document have a Page 7? I'm only asking because mine --
A. Mine has 5 and 6. Seven is just --
Q. Okay. If we highlight it on the screen, would that be okay for everyone?
A. That's fine for me.
Q. Okay. And I apologize for that.
THE COURT: I'll let you highlight it on the screen. But since this is an admitted document, you need to supply that --
MS. JONES: Yes.
THE COURT: -- as part of the exhibit.
MS. JONES: Absolutely. We'll do that. I think it was just a printing issue.
BY MS. JONES:
Q. So you see the conclusions there in the clinical study report. Do you see that, Doctor?
A. Could I have it blown down low first so I can see what's above it just so I can orient?

Q. Oh, sure.
A. Okay. That's good. Thank you.
Q. Okay.
Thank you, Mr. Reynolds.
Do you see there's a conclusion section and it says, "Exposure data," and there's a reference there to AUC. Do you see that?
A. Yes.
Q. And that's a reference to area under the curve; correct?
A. That's correct.
Q. "Exposure data of this trial showed that 75-milligram dabigatran etexilate twice daily is an appropriate dosing regimen for patients with severe renal impairment as the results compare favorably with the exposure levels seen for 150-milligram dabigatran etexilate twice daily in patients with moderate renal impairment."
Did I read that correctly?
A. You did.
Q. And then it goes on to say, "The pharmacokinetics of 75-milligram dabigatran etexilate twice daily observed in this trial were in good agreement with published pharmacokinetic models and the effect of dabigatran etexilate on coagulation in this study was in line with previous observations." Did I read that correctly?

A. You did.
Q. And it goes on to say at the bottom of the page, "In addition, twice daily administration of 75-milligram dabigatran etexilate for 7.5 days was safe and well tolerated by the patients with severe chronic kidney disease as defined by a creatine clearance between 15 and 30 milliliters per minute over the last three months before study participation in this trial."
Did I read that correctly?
A. You read it correctly.
Q. Okay. Are you aware that Boehringer Ingelheim actually did another also small study looking at the 75-milligram dose of, of Pradaxa after this study?
A. I'm not aware of a study for efficacy and safety long-term in AFib patients, but I believe that there is another shorter term study, yes.
Q. Okay.
MS. JONES: May I approach, Your Honor?
THE COURT: You may.
BY MS. JONES:
Q. Dr. Plunkett, you have in front of you what we have marked as Defense Exhibit 9191. Have you seen that exhibit before?
A. I don't know if I've seen it in this form, so let me look through it.

Q. Okay.

(Pause)

A. I don't know that I've seen this form, but I have seen -- some of the information in the back looks familiar. So maybe I've seen it in memos or something else.

Q. Okay.

MS. JONES: Your Honor, we would move for the admission of Exhibit 9191.

THE COURT: Any objection?

MR. MOSKOW: No objection.

THE COURT: It's admitted into evidence and may be published.

(Exhibit 9191 admitted into evidence.)

MS. JONES: Okay. Thank you, Mr. Reynolds.

Q. So, Dr. Plunkett, again just to situate ourselves, do you recognize this as a clinical trial report for a BI trial that was assigned a number 1160.173?

A. Yes, I see that.

Q. Okay. And you also see the title of the study, "A prospective open label study to evaluate the pharmacokinetics of dabigatran in NVAF patients with severely impaired renal function on dabigatran etexilate 75-milligram twice a day therapy."

Did I read that correctly?

A. You did, yes.

Q. And down at the bottom of the page you can see the date of the report, May the 24th, 2016; correct?
A. Yes.
Q. And it also shows the dates for the trial from July of 2013 until October of 2015; correct?
A. Yes.
Q. If we go to Page 2 of the document there is, much like the last report that we looked at, a section entitled "Objectives." I'll give you a chance to get to that.
A. I'm on 2, yes.
Q. And the objective is described as, "To assess dabigatran exposure at trough and peak in NVAF patients with severe renal impairment (defined as creatine clearance 15 to 30 milliliters per minute) receiving dabigatran etexilate 75-milligram BID therapy." Do you see that?
A. Yes.
Q. And so the purpose of this study was to look at Pradaxa exposure in atrial fibrillation patients who also had severe renal impairment and who were receiving the 75-milligram dose of Pradaxa twice a day; correct?
A. Yes.
Q. And then you can see there again the numbers for the study; correct?
A. Number of people? Yes.
Q. The number of people. So, again, this was a smaller

trial with 60 folks who were actually treated. Do you see that?

A. Yes.

Q. Okay. If you turn to Page 9 of this report, do you see the section entitled "Conclusions"?

A. I do.

Q. And it says, "The observed dabigatran plasma concentrations in patients with severe renal impairment following 75-milligram dabigatran etexilate (Pradaxa) twice daily were generally in agreement with those predicted by models developed from data in previous trials, although with a tendency towards under-prediction of median and higher concentrations."

Did I read that correctly?

A. You did, yes.

Q. And then it goes on to say, "The safety profile of Pradaxa, 75 milligrams twice daily in non-valvular atrial fibrillation patients with severe renal impairment in this trial was consistent with the patient population and the known safety profile of the drug with no unexpected safety concerns." Do you see that?

A. I do.

Q. Did I read that correctly?

A. I see it. And, yes, I agree you read it correctly.

Q. I threw a lot of questions at you at the same time. I

apologize. And that's just a way of saying in this small trial that the company had done that the safety profile of the medicine didn't show anything different than what the company already understood; correct? That's what it means by "no unexpected safety concerns."

A. I would assume that's what they're talking about. If you want me to confirm, I'd have to look in more detail, but --

Q. Let's finish up the discussion of the conclusions. "These findings suggest that Pradaxa 75-milligram twice daily is an appropriate dosing regimen for patients with severe renal impairment."

Correct? Did I read that correctly?

A. You read that correctly.

Q. Okay. Now, part of the role of the FDA is after a medicine like Pradaxa is approved, the agency continues to have responsibility for oversight of the medicine; correct?

A. Yes. The company continues to have a responsibility as well as the agency for oversight, yes.

Q. Absolutely. The company has a responsibility for keeping track of what's going on with the medicine. The FDA by virtue of its function as a public health agency responsible for prescription medicines in the United States also keeps track of what's going on with the medicine that it approves; correct?

A. Yes. Not as well as the company, but they do.
Q. Understood. Okay. And as far as you know, based on reviewing the documents for this case, is it your understanding that the FDA has continued to evaluate Pradaxa ever since its approval back in 2010 for atrial fibrillation patients?
A. So I'm -- you'll need to be more specific what you mean by continue to evaluate. Are you asking me about just within the drug safety group or within the entire group?
Q. Well, let's say drug safety as an example. Do you understand it to be the case that the FDA has continued to evaluate the safety of Pradaxa over the time that the medicine has been on the market?
A. Yes, there has been some evaluation.
Q. Okay. And as far as you know, there have been points after the approval of Pradaxa back in 2010 where the FDA has actually issued Drug Safety Communications regarding Pradaxa describing its analysis of some of the reports that the agency receives on adverse events with Pradaxa; correct?
A. Yes, that is true.
MS. JONES: May I approach, Your Honor?
THE COURT: Yes, you may.
BY MS. JONES:
Q. Dr. Plunkett, I've handed you a copy of what we've marked as Defense Exhibit 5831. Do you recognize Exhibit

5831?

A. Yes.

Q. Okay.

MS. JONES: Your Honor, we would move for the admission of Exhibit 5831.

THE COURT: Any objection?

MR. MOSKOW: No, Your Honor.

THE COURT: It's admitted.

(Exhibit 5831 admitted into evidence.)

MS. JONES: If we could put that up on the screen. Thank you, Mr. Reynolds.

BY MS. JONES:

Q. Dr. Plunkett, just to situate ourselves in terms of what this document is, do you recognize this as what's known as an FDA Drug Safety Communication?

A. Yes.

Q. And do you recognize it as a Drug Safety Communication from the FDA concerning safety review by the agency of post-market reports of serious bleeding events with the anticoagulant Pradaxa?

A. Yes.

Q. And just so we're clear, Drug Safety Communications are statements written by the FDA that are intended to provide the public with easy access to important drug safety information. Do you understand that to be the purpose?

A. I believe that's what is stated on their web page, yes.
Q. Okay. So you have no reason to disagree with that?
A. No, huh-uh.
Q. Okay. And this particular Drug Safety Communication was actually released about a year -- a little over a year after Pradaxa was approved in the United States for atrial fibrillation; correct? Do you see there's a date of December 7th, 2011?
A. Yes, that's true.
Q. Okay. And that reference at the top of that document to safety review of post-market reports, just to give the jury context for this, the FDA as part of its role receives reports from doctors, from patients, from various sources about adverse events that occur with medicines; correct?
A. Yes. And a lot of it is also information that they require the company to send in too that they look at as well.
Q. Right. And companies like Boehringer Ingelheim, for example, have a responsibility under the FDA's rules and regulations to actually submit regular reports letting the FDA know about reports that the company has received of safety issues for this medicine; correct?
A. Yes.
Q. Okay. And so what the FDA is doing here is talking about its analysis of post-market safety reporting that's

come in since the medicine was approved in October of 2010; correct?

A. Yes.

Q. And it says in that very first paragraph if we scroll down a little bit, "The U.S. Food and Drug Administration is evaluating post-marketing reports of serious bleeding events in patients taking Pradaxa." Do you see that?

A. I do.

Q. And it goes on to say, "Pradaxa is a blood-thinning anticoagulant medication used to reduce the risk of stroke in patients with non-valvular atrial fibrillation, the most common type of heart rhythm abnormality."

Did I read that correctly?

A. You did.

Q. And, and just to be clear about the types of reports that the FDA is looking at here, these are reports that are coming from what's sometimes referred to as the real world. This is what happened -- this is what's happeing with the medicine after it's approved outside of a clinical trial setting; correct?

A. Many of them, yes. There are some that are going to be coming from additional clinical studies that were being done too. But I would agree that there's -- because some of the things that the company submitted, in fact, were from some additional studies. But, yes, I would agree that it's meant

to be an assessment of what happens once you get a wider exposure to the drug and other kinds of people.

Q. And so, for example, with respect to this Drug Safety Communication, it would be reflecting on reports that might have been received from patients who were on the 150 dose of the medicine or patients who were on the 75-milligram dose of the medicine; correct?

A. Yes.

Q. The Drug Safety Communication goes on to say, based on the FDA's review of these post-market reports of serious bleeding events, "At this time FDA continues to believe that Pradaxa provides an important health benefit when used as directed and recommends that healthcare professionals who prescribe Pradaxa follow the recommendations in the approved drug label."

Did I read that correctly?

A. You did.

Q. Okay. And then a little further down it says -- there's a reference there to bleeding. Do you see that paragraph? We can call it out for you.

A. Yes.

Q. Do you see that? It says, "Bleeding that may lead to serious or even fatal outcomes is a well-recognized complication of all anticoagulant therapies."

That's true; right?

A. Yes.
Q. It goes on to say, "The Pradaxa drug label contains a warning about significant and sometimes fatal bleeds."
That's true; right?
A. Yes.
Q. And over in the, in the box there -- do you see there's a box that's called "Facts about Pradaxa"?
A. Yes.
Q. And it says it's a blood thinner; right?
A. Yes.
Q. And it says that it was approved to reduce the risk of stroke in patients with atrial fibrillation; correct?
A. Yes.
Q. It says that it's available in two doses, the 75-milligram and the 150-milligram; correct?
A. Yes.
Q. And then it actually provides information of approximately how many prescriptions of Pradaxa had been dispensed by this point in time when the FDA was looking at post-marketing safety reports. Do you see that?
A. Yes.
Q. A total of approximately 1.1 million Pradaxa prescriptions were dispensed and approximately 371,000 patients received Pradaxa prescriptions.
Then if you turn to the third page of that Drug Safety

Communication, the FDA concludes by saying at the top, "For patients with severe renal impairment, follow the recommended doses." Do you see that?

A. Yes.

Q. "For patients with creatinine clearance of 15 to 30 the recommended dose is 75 milligrams orally twice daily." Correct?

A. That's what is stated, yes. You read it --

Q. And -- I didn't mean to interrupt you. Sorry.

A. That's okay. If what you're asking is if you read it correctly, yes, you did.

Q. Yes. And that's the dose that the FDA approved for patients with severe renal impairment; correct?

A. Yes.

Q. And then it goes on to say there are no dosing recommendations for patients whose creatinine clearance is lower than 15; correct?

A. Yes.

Q. Okay. The last reference there in that little section is to reporting of adverse events. Do you see that?

A. Yes, yes, I see it.

Q. And that's just a reference to the type of reporting that we were talking about earlier; that the FDA has a mechanism for people to report adverse events to the agency. Correct?

A. Yes.
Q. Dr. Plunkett, are you aware, based on your review of the documents in this case, that after the FDA issued this Drug Safety Communication in 2011 that it then issued a separate Drug Safety Communication in 2012?
A. Yes.
MS. JONES: May I approach, Your Honor?
THE COURT: Yes, you may.
BY MS. JONES:
Q. Dr. Plunkett, I've handed you what we have marked as Defense Exhibit 5105. Do you recognize that document?
A. I do.
Q. Okay. And do you recognize it as the Drug Safety Communication that was issued by the FDA in November of 2012?
A. Yes.
Q. Okay.
MS. JONES: Your Honor, we'd move for the admission of Defense Exhibit 5105.
MR. MOSKOW: No objection.
THE COURT: It's admitted and may be published.
(Exhibit 5105 admitted into evidence.)
MS. JONES: Thank you, Your Honor.
BY MS. JONES:
Q. And, again, just to get ourselves situated in the

document here, do you see up at the top there's a reference to FDA Drug Safety Communication? Do you see that?

A. I do.

Q. And it's providing an update on the risk for serious bleeding events with the anticoagulant Pradaxa. Do you see that?

A. I do.

Q. And so this would have been roughly two years after Pradaxa was approved by the FDA for atrial fibrillation patients; correct?

A. Yes.

Q. And, again, this type of Drug Safety Communication is based on the FDA's review of post-marketing reports of bleeding events in what we referred to earlier as the real world, folks who are using the medicine largely outside of the clinical trial setting; correct?

A. Yes.

Q. If we go a little further down, there is a description of what the agency was doing in this safety announcement starting with the date there of November the 2nd, 2012. Do you see that?

A. I do.

Q. It says, "The U.S. Food and Drug Administration has evaluated new information about the risk of serious bleeding associated with the use of anticoagulants (blood thinners)

dabigatran (Pradaxa) and warfarin." And it refers to some other names for warfarin.

"Following the approval of Pradaxa FDA received a large number of post-marketing reports of bleeding among Pradaxa users."

Do you see that?

A. Yes.

Q. And that the agency, because it saw a large number of post-marketing reports of bleeding among Pradaxa users, it specifically wanted to evaluate whether there was something going on out in the real world that they might not have been fully sensitive to when the medicine was initially approved in 2010; correct?

A. Yes.

Q. And so this Drug Safety Communication actually describes an assessment that the FDA did to look at that specific question; correct?

A. Yes.

Q. And at the end of that paragraph it says, "FDA is continuing to evaluate multiple sources of data in the on-going safety review of this issue." Do you see that?

A. I do.

Q. Okay. And then a little further down in that next paragraph it says, "Pradaxa and warfarin are important medications used to reduce the risk of stroke and blood

clots in patients with non-valvular atrial fibrillation, the most common heart rhythm abnormality which causes the heart upper chambers or atria to beat rapidly and irregularly."

Did I read that correctly?

A. You did.

Q. And it goes on to say, "Although these drugs reduce the number of strokes in patients with non-valvular AF, they can cause bleeding, potentially leading to serious or even fatal outcomes." Do you see that?

A. Yes.

Q. And that's a true statement as to both Pradaxa and warfarin; correct?

A. Yes.

Q. And then later in time there were additional medicines that were studied and approved as alternatives to warfarin called Xarelto and Eliquis; correct?

A. Yes.

Q. And those medicines carry the same well-recognized risk of bleeding from anticoagulant treatment; correct?

A. Yes. All in this class would have that risk.

Q. Okay. And it goes on to say in the next paragraph, "FDA has not changed its recommendations regarding Pradaxa. Pradaxa provides an important health benefit when used as directed." Correct?

A. I agree that's there, yes.

Q. Okay. And, again, this would have been the FDA looking at adverse event reports that could have come from patients on the 150 and from patients with severe renal impairment who were on the 75-milligram dose; correct?

A. Yes.

Q. Okay. And at no point in this communication do they say two years out from approval of the medicine we think there's something going on with patients with severe renal impairment who are on the 75 that gives us concern. Correct?

A. No. They have some other statements in a document that came out from this, but that's not -- that statement would not be there.

Q. Okay. If we turn to Page 2 of the document, you can see there's a section called "Additional information for healthcare professionals." Do you see that?

A. Yes.

Q. And there are several bullets there, some of which include information about the use of the medicine; correct?

A. Yes.

Q. And, for example, the fourth bullet refers to the fact that Pradaxa is eliminated by the kidneys. Do you see that?

A. I do.

Q. And it says, "Renal function should be assessed prior to treatment with Pradaxa to determine the appropriate

dose." Correct?
A. Yes.
Q. And we, we saw that in the labeling for Pradaxa yesterday, correct, in the physician's label?
A. Yes, we did.
Q. And then there's another statement that renal function should be reassessed during treatment with Pradaxa if clinically indicated. Do you see that?
A. Yes.
Q. And the dose should be adjusted following the recommendations in the drug label.

And then the FDA goes on to say in the sixth bullet that for patients with severe renal impairment it continues to recommend 75 milligrams twice daily for patients with creatinine clearance of 15 to 30 milliliters per minute; correct?
A. Yes, that is there.
Q. That's the, that's the severely renally impaired patient population; correct?
A. Yes.

THE COURT: We'll need to take a break soon.

MS. JONES: I'm finished with that document so this might be an appropriate time.

THE COURT: All right. We're going to take a ten-minute recess. You may retire to the jury room.

(Recess taken from 10:37 a.m. until 10:46 a.m.)

THE COURT: Ms. Jones, do you have an idea yet how much longer you're going to be with --

MS. JONES: I might run a little past lunch.

THE COURT: Okay. Well, I don't mind going a little past noon if you're getting close, so between 12:00 and 12:15. Okay?

MS. JONES: Yes, of course.

THE COURT: All right. Let's bring the jury in.

(Jury returned into the courtroom at 10:48 a.m.)

THE COURT: All right. Be seated.

You may resume your examination.

MS. JONES: Thank you, Your Honor.

BY MS. JONES:

Q. Dr. Plunkett, when we took our break we were just finishing up our discussion of the two drug safety communications that the FDA had done.

THE COURT: Is your microphone on?

MS. JONES: It's showing green, Your Honor. It's -- my jacket is sliding a little.

BY MS. JONES:

Q. Let me start my question again. When we took our break we were having a discussion about the two drug safety communications that the FDA had issued in 2011 and 2012 related to Pradaxa and warfarin and bleeding rates on those

medicines; correct?

A. Yes.

Q. And just to close the loop on that discussion, one of the observations that the FDA made was that when it was looking at those two sets of bleeding between patients who were on warfarin and patients who were on Pradaxa, it had reviewed that just doing a simple comparison between the two would not be entirely accurate because warfarin is a well-known medicine and folks are a little more used to it. And with newer medicines you sometimes see higher reports of bleeding. Correct?

A. I don't think we read that part in here, but I'm aware that there is such discussion --

Q. Okay.

A. -- generally.

Q. Why don't we look at the document very quickly just so we can pin that point down. On Page 2 of 5105, do you see that? There's a section entitled "Data Summary."

A. I do.

Q. And the second paragraph of that section reads, "FDA believes that a simple comparison between Pradaxa and warfarin with respect to the numbers of post-marketing reports of bleeding in the AERS database is misleading because bleeding events associated with warfarin (a well-recognized consequence of warfarin use which has been

available for many years) are likely underreported compared to events occurring with the more recently available Pradaxa." Do you see that?

A. I do.

Q. And the FDA said, "FDA continues to evaluate multiple sources of data in the on-going safety review of this issue." Correct?

A. Yes.

Q. And that review would have included patients who were on the 150-milligram dose of Pradaxa and patients with severe renal impairment who were being prescribed the 75-milligram dose of Pradaxa; correct?

A. Yes. If they reported a bleed, both would be captured.

Q. Okay. And in this Drug Safety Communication, based on its evaluation of those, those reports between warfarin patients who had bleeds and Pradaxa patients who had bleeds, the FDA said very clearly it had not changed its recommendations regarding Pradaxa; correct?

A. That's true.

Q. Okay. And in the eight years since Pradaxa was approved, including at a 75-milligram dose for patients with severe renal impairment, the FDA has never changed its view that that dose is the appropriate dose for patients on Pradaxa with severe renal impairment; correct?

A. I can't tell you they haven't changed their view, but I

agree there's been no labeling change required by the FDA.
Q. Okay. Dr. Plunkett, are you aware that in addition to the FDA looking at Pradaxa over the course of the medicine's time on the market that there have also been studies done by scientists out in the world looking at the use of Pradaxa in patients who are prescribed the medicine?
A. Generally, yes, there have been reports in the literature.
Q. Okay. And are you aware of studies that have specifically looked at populations of patients that included patients on the 75-milligram dose?
A. Yes, there are some that include that.
Q. Okay. And do you know that there are actually studies that have specifically looked at Pradaxa 75-milligram versus one of the other anticoagulants, Xarelto?
A. So you'll need to show me. I'm not sure I know which study you're referring to.
Q. Okay. I'm going to show you a couple of papers.
MS. JONES: May I approach, Your Honor?
THE COURT: Yes, you may.
BY MS. JONES:
Q. Dr. Plunkett, I've handed you what we've marked as Defendant's Exhibit 5747. Do you recognize that exhibit?
A. Yes, I have seen this.
Q. Okay. And do you recognize it as a paper that reflects

the analysis of doctors both who work at the company, Boehringer Ingelheim, but also external scientists looking at the use of Pradaxa after its approval in 2010?

A. Yes, but I thought we were talking about the Xarelto study.

Q. That's our, that's our next exhibit.

A. Oh, okay. That's fine. That's great.

Q. Is that how you understand this, this is a paper that reflects analysis of the use of Pradaxa after its approval?

A. Yes, that is true.

Q. Okay.

MS. JONES: Your Honor, we would move to publish Exhibit 5747 for demonstrative purposes.

THE COURT: All right. You both are using the reference to demonstrative evidence. Is this a learned treatise?

MS. JONES: It is, Your Honor.

THE COURT: All right. You may proceed.

Let me just explain that to the jury. There are sometimes documents, reports, publications that are recognized by the parties as being authoritative in the field of whatever it discusses.

And in the examination of expert witnesses, parties are allowed to ask experts about specific statements in these learned treatises. And those statements become evidence

that you can use in evaluating the expert's opinions and testimony.

But the full report itself is not evidence in the case and will not be admitted as an exhibit. It won't be subject to the jury being able to look at it and consult it. So the important facts are what counsel points out in the examination of the expert and the statements in the report.

Go ahead.

MS. JONES: Thank you, Your Honor.

Is there any objection to us putting that on the screen?

MR. MOSKOW: There's no objection. We'll take them case by case.

MS. JONES: Okay.

BY MS. JONES:

Q. Dr. Plunkett, do you recognize on the screen there Exhibit 5747?

A. Yes, I have seen this before.

Q. Okay. And that's a paper entitled "A comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrillation patients in a large healthcare system." Do you see that?

A. Yes.

Q. Okay. And you see there are a listing of authors that appear immediately below the title of the paper?

A. Yes.
Q. And if you look right under that list of names, some of those individuals are affiliated with external research institutions like the Walter Reed National Military Medical Center for example. Do you see that?
A. Yes. Dr. Villines lists that.
Q. And then you can see that one of the authors on the paper is someone who worked at Boehringer Ingelheim, Janet Schnee. Do you see that?
A. Yes. And there's one other, Kimberly Siu.
Q. Okay, right. And then you see that this was a paper that the company participated in providing financial support for. Do you see that under "Financial Support"?
A. Yes. It's another down here further.
Q. There's a gray box towards the bottom.
A. Yes, under the -- on the summary down a little further.
Q. On the right-hand side.
A. Yes.
Q. Okay. And you see this was a paper that was published in 2015?
A. Yes, it was.
Q. And there's a, there's a summary that appears on the first page that actually describes the purpose of the study. Do you see that?
A. Yes.

Q. It says, "This study aimed --" this is about two sentences in from the beginning.
A. Okay.
Q. "This study aimed to compare the safety and effectiveness of dabigatran and warfarin in clinical practice."
Did I read that correctly?
A. You did.
Q. And that's just a simple way of saying we were looking at the safety and how well it worked for dabigatran or Pradaxa and warfarin out in the real world in clinical practice; correct?
A. Yes.
Q. Okay. Then it goes on to say, "We undertook a propensity score matched cohort study with 12,000 or so patients in each group." Correct?
A. Yes.
Q. So all told about 25,000 patients; correct?
A. I believe that's correct. If you want the exact -- yeah, that's what it says, yes.
Q. Roughly. And then it goes on to say, "Comparing treatment with dabigatran or warfarin in the U.S. Department of Defense claims database, October, 2009 to July of 2013." Do you see that?
A. Yes.

Q. And so what that refers to is the study is based on data on patient experience that was drawn by a claims database maintained by the Department of Defense; correct?
A. Yes.
Q. And that was like actual patient experience on those medicines; correct?
A. Yes.
Q. Okay. If we go to Page 6 of Exhibit 5747, do you see that there's a discussion there of how many of the Pradaxa patients were on the 150-milligram dose versus how many were on the 75-milligram dose? It's in the parentheses.

The sentence says, "Within the matched dabigatran group 87.6 percent of patients had prescriptions for the 150-milligram dose on the index day."

And then in the parentheses there it says 150-milligram, N equals 11,212. So that means there were 11,000 or so patients on the 150 in the study; correct?
A. Yes.
Q. And then it goes on to say that there were about 1,500 patients on the 75-milligram dose who were included in the study; correct?
A. Yes, that's what it stated.
Q. Okay. Now, it goes on to say right after that sentence we just looked at laying out the numbers of patients on each dose, "The overall size of the 75-milligram subgroup did not

meet the pre-specified protocol specified power threshold for a separate subgroup analysis." Do you see that?

A. Yes.

Q. And what that means -- I'm going to try to put it simply and you can tell me if I've got it right or wrong -- is that the number of patients who were on the 75-milligram dose, there weren't enough of them to be able to support from a statistical perspective an analysis for that particular subgroup; correct?

A. Yes, with the issue that the statistics had to be able to show that there was a difference between it -- that dose and 150 as compared to each other on safety and efficacy.

Q. And so what they ended up doing -- and we'll look at some of the data in a separate document -- is they actually combined all the patients who were on Pradaxa. They combined the 150 and the 75-milligram dose; correct?

A. Yes.

Q. For the patient -- for the Pradaxa side of the analysis; is that right?

A. That's correct.

Q. Okay. Now, have you been able to look at the supplemental tables that show the outcomes on this study?

A. Yes. In fact, it helps you understand more details.

Q. Okay.

MS. JONES: May I approach, Your Honor?

THE COURT: You may.

BY MS. JONES:

Q. Dr. Plunkett, I've handed you a copy of what we've marked as Defense Exhibit 5991. Do you see that?

A. Yes.

Q. And do you recognize that as the supplemental material to the Villines study that we were just looking at comparing warfarin and dabigatran in clinical practice?

A. Yes.

Q. And just so it's clear for the jury, sometimes when you have studies that are done, the data might not appear in the primary article sometimes. The authors will publish it in a separate supplement so you can see all the tables. Correct?

A. Yes, that's true.

Q. If you turn to Page 14 of Exhibit 5991, I just want to ask you a couple of questions.

MR. MOSKOW: No objection, Your Honor.

THE COURT: All right. Is this a demonstrative?

MS. JONES: It would be for demonstrative purposes, Your Honor.

THE COURT: All right.

MS. JONES: I was just trying to get her to the page.

THE COURT: Okay.

MS. JONES: And I apologize. Are we okay to

publish that?

THE COURT: Yes.

MS. JONES: Okay.

BY MS. JONES:

Q. Dr. Plunkett, do you recognize on Page 14 the information that's reflected showing primary and secondary outcomes for dabigatran or Pradaxa versus warfarin?

A. Yes, I do.

Q. Okay. You can actually see the title up at the top for the table. You can see "Supplement Table 5, hazard ratios for primary and secondary outcomes dabigatran versus warfarin with combined 150, 75-milligram population, and 150-milligram subgroup." Do you see that?

A. I do.

Q. And so just, just so we're clear about this, what the authors did because of what we talked about earlier in terms of the size of the 75-milligram group was they did an analysis of Pradaxa 150 versus warfarin and they also did an analysis of Pradaxa 150 and Pradaxa 75 together versus warfarin. Correct?

A. Yes.

Q. And I just want to look at a couple of the outcomes that are reflected up at the top of this chart if we could just call out the first four lines.

And, Doctor, just to situate ourselves in terms of what

this shows, you see here that there are a listing of outcomes on the left-hand side; correct?

A. Yes.

Q. And one of the outcomes that they looked at were patients who had stroke; correct?

A. Yes.

Q. And then one of the other outcomes were patients who had major bleeding; correct?

A. Yes.

Q. Okay. And if you look at the numbers that appear here, these reflect what are described as unadjusted HR or hazard ratios; correct?

A. Yes.

Q. And just give us a nutshell definition of what a hazard ratio is.

A. It's a value that quantifies the differences that may exist or not and the risks of the two populations being compared.

So a change in the hazard ratio either above one or less than one has an effect on how you interpret the data. If the hazard ratio is exactly one, there would be no difference between those two groups you're comparing on risk.

Q. Okay. And so for, for the two categories that we have here, we can see what you just described as the hazard ratio

for the 150-milligram and 75-milligram Pradaxa population when it was compared to warfarin; correct?

A. Yes.

Q. And if you look at the stroke outcome and the major bleeding outcome, both of those hazard ratios are under one; correct?

A. The average -- yeah, the actual HR value, yes, that's true.

Q. Yes, under one. And so that means there were fewer of those events on Pradaxa including the 150 and the 75-milligram dose than there were on warfarin?

A. There were numerically fewer, yes.

Q. Okay. And if you look over at just the 150-milligram results, the hazard ratios when you compare just 150 of Pradaxa versus warfarin, the numbers are almost the same; correct? Those hazard ratios are almost the same; correct?

A. As the ones for the combined, yes.

Q. Yes.

A. Those -- the actual calculated number is very similar.

Q. Okay. And so the presence of the 75-milligram dose in that first group that we were talking about, that didn't cause any change in the outcome results that were reflected relative to the patients who were evaluated who were just on the 150-milligram dose; correct?

A. Based on just that comparison, those numbers are

similar. I would agree.

Q. Okay.

If we could take that down, Mr. Reynolds.

Now, Dr. Plunkett, I earlier mentioned -- I had earlier asked you whether you were aware of studies that have looked at the Pradaxa 75-milligram dose versus patients who were taking Xarelto, or lower dose of Xarelto. Do you remember that question?

A. Yes.

Q. Okay. And I confess I don't remember whether you said you had seen it or you hadn't seen it.

A. Well, I've seen some studies, but I don't know -- there's some observational kind of epidemiological research if that's what you're talking about. I am aware of some of that.

Q. Okay.

A. I asked you if you'd show me maybe I can confirm.

Q. I will show you, absolutely.

MS. JONES: May I approach, Your Honor?

THE COURT: You may.

MR. MOSKOW: Your Honor, may we have a sidebar, please?

THE COURT: Yes.

(Bench conference, reported.)

MR. MOSKOW: I'm not exactly sure where I'm

supposed to be.

We have concerns about going into comparison to Xarelto. There's no evidence in the record that they ever considered Xarelto as a potential treatment option. And the only mention of Xarelto has been raised by counsel during cross-examination.

So I think it's inappropriate to now challenge the expert on an area that is not under consideration in this case.

MS. JONES: Two quick responses, Your Honor.

The first is there was a very stark claim made yesterday that the 75 has never been studied, that no one's ever looked at it. We have no data on patients who were on the 75. This paper demonstrates that in the real world there have been scientists and doctors who have looked at the 75.

THE COURT: For Pradaxa?

MS. JONES: For Pradaxa, yes. And they've looked at it in connection with comparing it to patients who were on the lower dose of Xarelto. So that's the first point.

The second point is that Dr. Plunkett made a point yesterday of saying, well, at a certain point in time there were other options for patients beyond, beyond Pradaxa.

And I think there will be a suggestion for Mrs. Knight in particular that at a certain point in her treatment on

Pradaxa that maybe her doctors could have considered something else.

And I do think we're going to be left in a situation where discussion of whether she could have been moved to Xarelto or Eliquis will come up in the case.

MR. MOSKOW: Your Honor, the only evidence in this case is that she was on warfarin and her family saw an ad and asked her to be switched to Pradaxa. There's no consideration --

THE COURT: I'm going to take these things as they arise. Here the exhibit that you're about to discuss with the witness purports to show a comparison between Pradaxa and Xarelto.

MS. JONES: Uh-huh.

THE COURT: I'll allow it.

(Bench conference concluded)

MS. JONES: May I proceed, Your Honor?

THE COURT: You may.

BY MS. JONES:

Q. Dr. Plunkett, I think I handed you Exhibit 5526. Do you have that?

A. I do.

Q. And do you recognize Exhibit 5526?

A. Yes, I've seen this before.

Q. Okay. And before we put it up on the screen, do you

recognize it as an analysis done by, among others, doctors and scientists at the Food and Drug Administration looking specifically at patients who were on the lower dose of Pradaxa versus patients who were on Xarelto?

A. I see 150 milligrams of dabigatran versus 20 milligrams of Xarelto.

Q. Okay.

A. Is that what you're talking about? That would be the 75 specifically.

Q. Well, do you understand that this, this paper actually specifically analyzed outcomes for patients on the lower dose of Pradaxa versus patients on the lower dose of Xarelto?

A. There's some data, but their conclusions are based on the 150 versus Xarelto.

Q. Okay.

MS. JONES: Well, Your Honor, we'd move for the ability to, to display to the jury Exhibit 5526 under the framework we talked about before.

THE COURT: You may proceed.

MS. JONES: Okay.

BY MS. JONES:

Q. Okay, Dr. Plunkett, just again to get ourselves situated, up at the top here you see the title of the paper is "Stroke, bleeding, and mortality risks in elderly

Medicare beneficiaries treated with dabigatran or Rivaroxaban for non-valvular atrial fibrillation." Do you see that?

A. I do.

Q. And just to be clear, those references to dabigatran or Rivaroxaban, those are just names for Pradaxa and Xarelto; correct?

A. Yes.

Q. Okay. And if you look right under the title of the paper, there is a reference there to individuals who, among others, worked at the FDA; correct?

A. Yes.

Q. Including Dr. David Graham who is a senior member of the FDA team; correct?

A. In the drug safety group, yes.

Q. Okay. And if we look down at the bottom of Page 1 of Exhibit 5526, we can actually see there's a reference to "Author Affiliations" are listed at the end of this article. Do you see that there?

A. Yes.

Q. And if we go to the end of the article on Page 9 of 5526 -- are you there, Doctor?

A. Yes, I am.

Q. -- there is a section entitled "Author Affiliations." Do you see that?

A. Yes.
Q. And if you look through the list there, there are folks who are affiliated with the FDA. For example, the first reference is to the Office of Surveillance and Epidemiology Center for Drug Evaluation and Research. Do you see that?
A. Yes.
Q. And then it lists the names in parentheses of the names of the folks who worked there; correct?
A. Yes.
Q. And then there are people who work at other institutions. So, for example, there's a reference to someone who worked at the Department of Economics at Stanford University. Do you see that at the bottom?
A. Yes.
Q. Okay. If we go back to the first page of Exhibit 5526, do you see there is a section that's entitled "Objectives"?
A. Yes.
Q. It says, "To compare risks of thromboembolic stroke, intracranial hemorrhage, also known as ICH, major extracranial bleeding including major gastrointestinal bleeding and mortality in patients with non-valvular atrial fibrillation who initiated dabigatran or Rivaroxaban treatment for stroke prevention." Did I read that correctly?
A. You did.

Q. Okay. And just to break that down, the authors here were looking to compare patients on Pradaxa versus patients on Xarelto in terms of their risk of stroke, brain bleeds, or what is described here as major extracranial bleeding, so bleeding outside of the brain. Correct?

A. Yes.

Q. And they're also looking at mortalities; correct?

A. Yes.

Q. If you go to Page 16 of your exhibit, do you see that there's actually a table there that refers to analysis that was done of outcome event counts and adjusted hazard ratios with 95 percent confidence intervals comparing inverse probability of treatment weighted new user cohorts treated with lower renal doses of dabigatran 75-milligram twice daily and Rivaroxaban, 15 milligrams once daily for non-valvular atrial fibrillation. Did I read that correctly?

A. You did.

Q. It's a mouthful. Is that saying very generally that they looked at patient outcomes for certain events and they compared specifically patients who were on the lower dose of dabigatran or Pradaxa, 75 milligrams twice daily, and they looked at patients who were on the lower dose of Xarelto? Is that a fair way to describe that?

A. Yes.

Q. Okay. And if we look at the actual table below, there's a column on the left that lists the specific events that they were considering; right?
A. Yes.
Q. And thromboembolic stroke is the first thing that they identified; correct?
A. They did.
Q. Okay. And what they said there was -- and then the next thing on the list, I'm sorry, the next thing on the list is intracranial hemorrhage; correct?
A. Yes.
Q. That's another way of referring to brain bleeds; correct?
A. Yes.
Q. And then there's a reference below that to major extracranial bleeding; correct?
A. Yes.
Q. And major extracranial bleeding is major bleeding that occurs outside of the brain; correct?
A. Yes.
Q. And then underneath that they broke out the numbers for major gastrointestinal bleeding; correct?
A. Yes.
Q. And then they broke out the numbers for death. Do you see that?

A. Yes.
Q. Now, when the, when the authors who conducted this study were doing so, they were using data from a Medicare database; correct?
A. Yes.
Q. And so, again, we're talking about patients using Pradaxa, using the 75-milligram dose of Pradaxa in the real world; correct?
A. Yes, that's what is indicated.
Q. Okay. And what the results of this analysis show if you just look at the numbers on the right-hand side in terms of what you described as the hazard ratios earlier is that the numbers are roughly the same -- they show roughly the same results for dabigatran 75 versus the Xarelto lower dose; correct?
A. Yes.
Q. And if we go back to the first page of this paper, this was a paper published in a journal that's a part -- under the umbrella of the American Medical Association; is that correct?
A. Yes.
Q. If you look down at the bottom of the page there's a copyright for the American Medical Association; correct?
A. Yes.
Q. And this was in 2016?

A. It was published then, yes.
Q. Doctor, I want to show you one other paper and then I'll move to another topic.
MS. JONES: May I approach, Your Honor?
THE COURT: You may.
BY MS. JONES:
Q. Dr. Plunkett, I've handed you what we have marked as Exhibit 9327. Do you recognize Exhibit 9327?
A. Yes, I have seen this before as well.
Q. Okay. And do you recognize it as a paper that compared stroke and bleeding risks for patients on Pradaxa and Xarelto and patients specifically who were on the lower doses of those medicines?
A. It wasn't just the lower doses, but there is a group of people on lower doses.
Q. Okay.
A. They're looking across the, the data which has much more for the higher dose. But certainly there are some patients in here in that group, yes.
MS. JONES: Your Honor, we would move for permission to publish that to the jury.
MR. MOSKOW: Based on the same explanation as to how it will be used.
THE COURT: All right. You may use it in your examination of the witness.

MS. JONES: Thank you, Your Honor.

BY MS. JONES:

Q. Dr. Plunkett, you can see up at the top of this journal article there's a description of the title "Comparing stroke and bleeding risk with Rivaroxaban and dabigatran in atrial fibrillation, analysis of the U.S. Medicare Part D data." Did I read that correctly?

A. Yes.

Q. And then it names two articles who were at the University of Pittsburgh. Do you see that?

A. I think you're right, yes.

Q. If we can scroll down to the bottom, Mr. Reynolds, very quickly.

Do you see there are footnotes there that show their affiliation with the University of Pittsburgh?

A. Yes, that's true.

Q. Okay. And then if we go back up to the left-hand column, there is a description of the objectives for the paper. Do you see that?

A. Yes, I see it.

Q. It says, "Our objective was to compare effectiveness and safety between Rivaroxaban 20-milligram versus dabigatran 150-milligram and Rivaroxaban 15-milligram versus dabigatran 75-milligram among patients with atrial fibrillation." Do you see that?

A. Yes.
Q. And, again, in short, and I think this is the point that you were making, there's data here comparing the higher doses of Pradaxa and Xarelto; correct?
A. Yes.
Q. And then there's data also captured in this study comparing real world experience of patients who were on the Pradaxa 75-milligram dose versus patients who were on the Xarelto 15-milligram dose; correct?
A. Yes, that's what they're attempting to do.
Q. Okay. And so in that, in that second group of patients who have the lower doses of those medicines, those are patients who have kidney problems; correct?
A. Well, that's the data. I can't confirm that they're all getting it for the right reason. That's a problem with all these papers. They don't -- when you look at it. But I would agree that by the label if they were being used that way, that's how it should be.
Q. Okay. If you look a little further down in that same column, there's a section entitled "Methods." Do you see that?
A. Yes.
Q. Okay. And I want to direct your attention to what appears to be the second sentence there. It refers to the sample size that was used. Do you see that?

A. Yes, I see that.
Q. It says, "Our sample included 7,322 patients receiving dabigatran 150 milligrams." That's the higher dose of Pradaxa; correct?
A. Yes.
Q. The study also included 5,799 patients receiving Rivaroxaban 20 milligrams; correct?
A. Yes.
Q. The study also included 1,818 patients who received a lower dose of Pradaxa, the 75-milligram; correct?
A. Yes.
Q. And then they also included patients who had received the lower dose of Xarelto. That's 2,568 patients. Correct?
A. That's correct.
Q. And if we go to Page 8 of the study, they actually talk about what they saw when they compared patients on Pradaxa and patients on Xarelto, including specifically patients on the lower doses of those medicines; correct?
A. Yes, they do report separate data.
Q. Okay. And on the left-hand side of the page there's a column that includes a -- I want to just read the tail end of the sentence here. It says, "There was no difference in the risk of ischemic stroke and intracranial bleeding between Rivaroxaban 15 milligrams and dabigatran 75 milligrams." Correct?

A. Yes.
Q. All right. And so what that means is there was no difference in the rates of stroke or brain bleeding between Xarelto, the lower dose, and Pradaxa, the lower dose; correct?
A. That is correct.
Q. Okay. But it goes on to say that the risk of other thromboembolic events all cause mortality, major bleeding, any bleeding event, and gastrointestinal bleeding was higher with Rivaroxaban 15 milligrams than with Pradaxa 75-milligram; correct?
A. That is what is stated, yes.
Q. And so just to make sure we understand what all those references are, a thromboembolic event is a clot that is, that occurs that is not an ischemic stroke basically.
A. Yes.
Q. It's everything else that involves that kind of event. "All cause mortality" refers to patients who died or passed away; correct?
A. Yes.
Q. Major bleeding refers to serious bleeding events; correct?
A. Yes. And they, they have a specific definition in here, yes.
Q. And then there's a reference to any bleeding event and

gastrointestinal bleeding; correct?

A. Yes.

Q. All right. And on those last set of factors, Pradaxa 75-milligram actually appeared to be better than Xarelto 15-milligram; correct?

A. As far as the hazard ratios, that's true.

Q. If we go back to the first page, this was another study that was done -- that was published in 2016; correct?

A. Yes.

Q. And this is a study that was published in a journal known as the *American Journal of Cardiovascular Drugs*. You can see that in the upper left-hand corner; correct?

A. Yes.

Q. And this is another example, like the one that we just looked at, the Graham paper, that reflects a study by scientists into the use of the 75-milligram dose of Pradaxa in the real world; correct?

A. That was the attempt, yes.

Q. Dr. Plunkett, I want to turn to a different topic and it's one that we started talking about a little bit yesterday which is the labeling for Pradaxa. Okay?

A. Okay.

Q. And I want to start with what I think you spent a fair bit of your time talking about yesterday, which is the Medication Guide for Pradaxa. Okay?

A. Okay.

MS. JONES: May I approach, Your Honor?

THE COURT: You may.

BY MS. JONES:

Q. Dr. Plunkett, I've handed you what we've marked as Exhibit 5884.

MS. JONES: And I'm told that that exhibit has already been admitted into evidence. So may we publish it, Your Honor?

THE COURT: You may. Do you recall what the number is of the corresponding -- the plaintiffs' exhibit?

MS. JONES: It's 5884. It came in during our play of Michelle Kliewer's deposition.

THE COURT: All right, very good.

BY MS. JONES:

Q. Okay. Dr. Plunkett, do you recognize on your screen there and in the hard copy version as well a copy of the labeling for the medicine Pradaxa?

A. Yes.

Q. Okay. And if we just look at the bottom right-hand corner of this section that we have called out here, you see that that's a version of the label dated January of 2012; correct?

A. Yes.

Q. And yesterday during our discussions we talked about

the fact that the label includes both a label for doctors at the front; correct?

A. Yes.

Q. And then at the back of the document there is a label that is prepared for patients, correct, on Page 11?

A. That's correct, Yes.

Q. Okay. And we're going to start with Page 11 in talking a little bit about the Medication Guide for Pradaxa.

Is it fair to say that, that the Medication Guide and the labeling for doctors that are made available by the company, those are both important pieces of information about the medicine?

A. Yes. And one is directed to the patient and one to the physician.

Q. Right. And both are approved by the Food and Drug Administration; correct?

A. Yes.

Q. Now, yesterday we talked about this first piece of information about the Medication Guide which it tells patients, "You should read this every time you pick it up." Correct?

A. Yes.

Q. And I think you said that was perfectly sensible advice to give patients; correct?

A. Yes.

Q. And then it goes on to say in this version of the Medication Guide, "What is the most important information I should know about Pradaxa?" Correct?
A. Yes.
Q. And in this version of the Medication Guide that first piece of information, the most important information is that Pradaxa can cause bleeding which can be serious and sometimes lead to death; correct?
A. Yes.
Q. Now, that's a true statement; correct?
A. Yes.
Q. And, and the statement actually goes on to explain why it is that Pradaxa can cause a bleed; correct?
A. Yes.
Q. It says this is because Pradaxa is a blood thinner medicine that lowers the chance of blood clots forming in your body; correct?
A. Yes.
Q. And that's a true statement; correct?
A. Yes.
Q. Okay. Now, that warning that I just read, that warning would apply to any oral anticoagulant; correct?
A. Yes.
Q. If we switched out the word "Pradaxa" for the word "warfarin," it would still be true; right?

A. Yes, that's correct.
Q. Okay. And that warning also is a warning that applies to every patient; correct?
A. Yes.
Q. It doesn't carve out certain groups of patients and say, "Well, this is not something you need to worry about." Right?
A. That's correct.
Q. And you agree that that's a strong warning; correct?
A. Yes.
Q. You agree that that's a serious warning; correct?
A. Yes.
Q. Okay. Now, the Medication Guide actually goes beyond just that general warning about the risk of potentially fatal bleeding. It talks about specific patient characteristics that might increase a patient's risk of bleeding; correct?
A. It has some of them here, yes.
Q. Okay. And it says, for example, you may have a higher risk of bleeding if you take Pradaxa. And then it lists various bullet points; correct?
A. Yes.
Q. The first one is if you're over 75 years old; correct?
A. Yes.
Q. And that's a true statement. If you are over 75 years

of age and you take Pradaxa, your risk of bleeding increases; correct?

A. Yes.

Q. The next bullet point there is if you have kidney problems and you take Pradaxa, that might increase your risk of bleeding; correct?

A. Yes.

Q. The next item is if you have stomach or intestine bleeding that is recent or keeps coming back or you have a stomach ulcer, that could increase your risk of bleeding if you're on Pradaxa; correct?

A. Yes, that's stated.

Q. And then it goes on to say if you take other medicines that increase your risk of bleeding and you're also taking Pradaxa, that could, that could cause you to have a higher risk of bleeding; correct?

A. Yes.

Q. And it then goes on to list some of the medicines that might increase the risk of bleeding in a patient who's on Pradaxa; correct?

A. Yes.

Q. For example, it mentions aspirin or aspirin-containing products; correct?

A. It does.

Q. It also mentions a medicine known as Plavix towards the

end of that list. Do you see that?
A. Yes, it does.
Q. And, and part of the reason that those medicines can increase your risk of bleeding if you're taking Pradaxa is because both of those medicines have their own risk of bleeding; correct?
A. Yes, different mechanization of action but, yes.
Q. And then on this issue of medicines and how they can increase your risk of bleeding, the Medication Guide actually tells patients be sure that you talk to your doctor about what medicines that you're taking; right?
A. Later on I think it does, yes.
Q. If you go past that last bullet, it says, "Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above." Do you see that?
A. Yes. I'm sorry. I was thinking there's another statement further on --
Q. There is --
A. But I agree that is there.
Q. I didn't mean to interrupt you. I apologize. There is another statement and we're going to look at that one too. But that's there. And I assume you don't take issue with that advice to patients. That's a sensible thing to advise patients to do, talk to your doctor if you're on any of

these medicines; correct?

A. Yes. Hopefully you would tell your doctor about all the medicines you're on.

Q. And, in fact, if we look back in the Medication Guide just to go to the point that you were making just a moment ago, on Page 12 of 5884 there's actually a section on what patients should do with respect to the medicines that they're taking towards the bottom of the page.

There is in bold print a statement that encourages patients, "Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements."

Did I read that correctly?

A. You did.

Q. And, again, that's a perfectly reasonable piece of advice to give to a patient in terms of safely using Pradaxa; correct?

A. Yes.

Q. And it goes on to say, "Some of your other medicines may affect the way Pradaxa works. Certain medicines may increase your risk of bleeding." Correct?

A. Yes.

Q. And then it refers back to that section we were just looking at entitled, "What is the most important information I should know about Pradaxa?" Correct?

A. It does refer back, yes.
Q. Going back to Page 11 of the Medication Guide, after telling patients this medicine could cause serious bleeding that could lead to death and after identifying patient characteristics that can increase that risk of bleeding, the Medication Guide goes on to explain in more detail how Pradaxa works and some other things that might happen while you're taking the medicine; correct?
A. Yes.
Q. So, for example, there's a bullet there that says, "Pradaxa can increase your risk of bleeding because it lessens the ability of your blood to clot." Do you see that?
A. Yes.
Q. And that's a true statement; correct?
A. Yes. And that's similar to what was above.
Q. Okay. It says, "While you take Pradaxa you may bruise more easily. It may take longer for any bleeding to stop." Correct?
A. Yes.
Q. And those are true statements; correct?
A. Yes.
Q. And, again, if we replace the word "Pradaxa" with "warfarin" or with the names of any of the other oral anticoagulants, those would still be true statements;

correct?
A. Yes.
Q. And then a little further down the Medication Guide tells patients, "Here are some things you should be looking out for and let your doctor know about while you're on the medicine." Correct?
A. Yes, the next section, yes.
Q. Yes. And it starts in bold text, "Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding." Do you see that?
A. I do.
Q. And then it specifically describes various signs or symptoms of bleeding including unexpected bleeding or bleeding that lasts a long time. Do you see that?
A. Yes.
Q. Bleeding that is severe or you cannot control. Do you see that?
A. Yes.
Q. And then it mentions a couple of things that may or may not mean that you're having a bleed but might suggest there's something going on that your doctor needs to check on like pink or brown urine or red or black stools. Correct?
A. Those are listed, yes.
Q. And those could potentially indicate that there is

somekind of internal bleeding event; correct?
A. Yes.
Q. And your doctor needs to check on you; right?
A. Yes.
Q. And then the rest of that list goes through some other things that patients just need to be looking out for while they're taking the medicine; correct?
A. Yes. Some of these are similar to the kinds of things that you would see if you're bleeding, but, yes.
Q. Okay. And, again, you don't have a criticism or take issue with this portion of the Medication Guide. This is reasonable advice to give to patients about how to safely use the medicine. Correct?
A. I don't know that I would put it quite that way, but I don't disagree that it's good that they understand what symptoms are there if they're bleeding --
Q. Okay.
A. -- that they would need to get attention for.
Q. Okay. If you turn to Page 12, there's a section entitled, "What is Pradaxa?" Do you see that?
A. I do.
Q. And that section tells patients Pradaxa is a prescription medicine used to reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation. Do you see that?

A. Yes.
Q. And that's a true statement; correct?
A. Yes.
Q. "With atrial fibrillation part of the heart does not beat the way it should. This can lead to blood clots forming and increase your risk of a stroke. Pradaxa is a blood thinner medicine that lowers the chance of blood clots forming in your body." Did I read that correctly?
A. You did.
Q. And those are all true statements; correct?
A. Yes.
Q. The Medication Guide goes on to tell patients, "What should I tell my doctor before I take Pradaxa?" Do you see that section?
A. Yes.
Q. It says, "Before you take Pradaxa tell your doctor if you, for example, have kidney problems." Do you see that?
A. Yes.
Q. Or if you've ever had bleeding problems; correct?
A. Yes.
Q. And then it lists some other things that patients should just be mindful of when they're talking to their doctors about the possibility of using Pradaxa; correct?
A. Yes, general things, yes.
Q. Then the other thing that the Medication Guide tells

patients is, "Tell all your doctors and your dentist that you're taking Pradaxa." Do you see that?

A. Yes.

Q. And that's because it's important that other doctors who might not be the ones who are prescribing your Pradaxa be aware of it so they know it when they're prescribing medicines or when they're performing procedures on you; correct?

A. Yes. It's mainly on the issue of -- this is mainly directed to the issue of surgeries and procedures. That's exactly right.

Q. And that's why they mention dentists for example. They want to make sure that when people go to the dentist to have somekind of procedure done that the dentist is aware that is a patient who's on a blood thinner that might cause bleeding to be more significant than it might be ordinarily; correct?

A. Yes, that's correct.

Q. And, again, you don't, you don't take issue with that advice when given to patients; correct?

A. No.

Q. And then at the bottom of the page, just to round out our discussion on the medicine issue, the very bottom of the page says, "Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine." Do you see that?

A. Yes.
Q. And, again, that's reasonable advice to give to patients; correct?
A. Yes.
Q. And then on Page 13, we don't have to go through all of these, but it basically gives patients some guidance on how to take the medicine. You can take it with or without food. You shouldn't break it out. You should always swallow it as one capsule, those types of things. Right?
A. Yes.
Q. And then it talks about possible side effects and refers to things beyond the bleeding that we've already talked about; right?
A. Yes.
Q. Down at the bottom of the page.
A. Yes, I agree.
Q. Okay. And then on the, on the final page of the Medication Guide at the very top of the page it tells patients, "These are not all of the possible side effects of Pradaxa." Did I read that correctly?
A. You did.
Q. Okay. And it says, "For more information, ask your doctor or pharmacist." Correct?
A. Yes.
Q. And it goes on to say, "Call your doctor for medical

advice about side effects." And then it gives patients information on how they can report side effects to the FDA. Correct?

A. Yes.

Q. And I think we talked about yesterday the fact that it's, it's reasonable to give that kind of advice to patients because Pradaxa is a prescription medicine that you can only get if a doctor or a healthcare professional with prescribing authority says, "This is the right medicine for you." Right?

A. Well, I would agree with these statements. I don't know if they have quite that discussion, but absolutely, yes, I agree it's reasonable to tell a patient to report their side effects, yes.

Q. And not just to report side effects, but to talk about possible side effects of Pradaxa, including side effects that might not be featured in the Medication Guide. That's what that recommendation is at the top of the page; correct?

A. Yes. It's recommending about ones that are not listed here. That's exactly right.

Q. Okay. If you look further down at the section called general information about Pradaxa you see there's a paragraph that says, "This Medication Guide summarizes the most important information about Pradaxa." Do you see that?

A. Yes.

Q. And it says, "If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for more information about Pradaxa that is written for health professionals." Correct?

A. Yes.

Q. And, again, that language is encouraging patients to talk to their doctors about their use of the medicine; correct?

A. Yes.

Q. And it also references the fact that there is additional information given by the company to doctors and healthcare professionals who prescribe medicine; correct?

A. Yes.

Q. And at the very bottom of the page there -- not the very bottom -- it says, "This Medication Guide has been approved by the U.S. Food and Drug Administration." Correct?

A. It does.

Q. The formatting of the Medication Guide, the font size, that's all regulated by the FDA; correct?

A. Yes, the general outline is, that is true.

Q. Okay. Now, doctors are separately given even more detailed information about the medicine in something that's sometimes referred to as the package insert or the physician's label; correct?

A. Yes.
Q. Okay. And that's the ten or so pages that appear at the front of Exhibit 5884; correct?
A. That is correct.
Q. All right. And, and yesterday when we were talking, we spent some time looking at the first page of this document. But I, I want to spend some time talking about it in more detail today.

But let me ask you a question just to start. Would you agree that unlike the Medication Guide, the label is written for doctors and other healthcare professionals who prescribe Pradaxa?
A. Yes, I agree that's true.
Q. Okay. Would you agree that it wouldn't be unusual to find more detailed, more technical information and language in the physician's label than what you might find in the Medication Guide?
A. I agree more detailed and technical details. Yes, I would expect to see that.
Q. Okay. And would you also agree that there is certain information that might be included in a label for a doctor that wouldn't be appropriate to be included in a Medication Guide that's intended to be written for patients?
A. I would agree it's possible, but I think it would be highly dependent -- my opinion would be highly dependent on

what that information was, but certainly it's possible.

Q. Now, I think the jury has now seen various versions of the Pradaxa label at different points in time. But just to be clear, the FDA had to give approval on the label for Pradaxa during the entire time that the medicine has been on the market; correct?

A. Yes, even though there's at least one case where the approval came after. But, yes, that's true. That is required by the process.

Q. Okay. And it's not uncommon over time -- it's common practice that labels can evolve over the course of a medicine being on the market; correct?

A. Yes.

Q. All right. Do you know how many updates there have been to the Pradaxa label in the last eight years since the medicine's been on the market?

A. I would say more than a dozen, but I haven't counted them.

Q. Okay, fair enough. Each one of those labels had to be approved by the FDA; correct?

A. Yes.

Q. Now, you agree that the FDA has among the many professionals who work there medical doctors who are involved in evaluating the drug labeling that companies propose to the agency; correct?

A. In general terms -- if you're asking me generally, that is true. That occurs.

Q. Just generally. And just to be very clear, in terms of the work that you're doing in this case, you have been testifying as an expert for plaintiffs' counsel in pharmaceutical product liability cases since 2003; is that right?

A. Yes. My first case was in 2003.

Q. Okay. So that's approximately 15 years; is that right?

A. Yes.

Q. Okay. You've never -- during that 15-year period you've never testified for a manufacturer or a company in a products liability case; right?

A. Not in product liability, that is true.

Q. Okay. And you have never testified in a product liability case that a manufacturer of a medicine like Boehringer Ingelheim acted reasonably; correct? You've never testified to that in 15 years?

A. Probably true, but not all my cases have to do with that issue. But the ones where it has, yes, that would be true.

Q. To the extent that you've been asked to evaluate that issue over the course of 15 years, you've never concluded that a company acted reasonably; correct?

A. Based on the facts I have seen, that is true.

Q. Okay. And to go back to this issue of, of labeling and warnings, in those 15 years you've never testified at a deposition or in court that the warnings that a company gave were appropriate; right?

A. Again, with the same limitation that's not always what I'm doing. Sometimes it's limited. But in the cases where that's an issue, yes, absolutely, that's the things I would be talking about.

Q. Okay. But -- now, that's been your work as a litigation expert. But out in the real world you've never been asked by the FDA, the Food & Drug Administration, to give opinions about a label for a medicine, have you?

A. No. And they typically would not do that.

Q. Okay. You've never drafted an entire label for a medicine?

A. No, I have not.

Q. Okay. And even though you're here as a regulatory expert in this case, you didn't look at the full regulatory record for Pradaxa, did you?

A. No, because I didn't believe it was all relevant to the work I was doing.

Q. Okay. And you didn't review all of the correspondence between Boehringer Ingelheim and the FDA as it relates to Pradaxa, did you?

A. Not for the entire history of the drug, although I did

ask for the entire correspondence at certain periods of time based on the work I was doing.

Q. Okay, all right. Let's talk -- you didn't go through the detail in a physician labeling for Pradaxa, but I want to spend some time talking about that with you in the time we have before lunch and probably carrying over after.

We've talked about the first page and I just want to touch on one point there and then we'll get into some more of the details.

There is a section on the first page in the highlighted section of the label entitled "Warnings and Precautions." Correct?

A. Yes.

Q. And that first warning is, "Pradaxa can cause serious and sometimes fatal bleeding. Promptly evaluate signs and symptoms of blood loss." Correct?

A. Yes.

Q. And, again, just like the Medication Guide, that's a warning that applies to every patient who takes Pradaxa; correct?

A. Yes.

Q. And you would agree, just as you agreed with respect to the Medication Guide, that that warning is a strong warning; correct?

A. Yes.

Q. It's a serious warning; correct?
A. Yes.
Q. And we talked yesterday about these little numbers that are in the parentheses at the end of some of these references. Those are references to different sections in the label; correct?
A. That's correct.
Q. Okay. Now, is it true that that warning, Pradaxa can cause serious and sometimes fatal bleeding, that warning has been given to doctors by Boehringer Ingelheim for every day that the medicine has been on the market?
A. Yes. It was in the launch label doctors are referring to.
Q. Okay. And that's, that's a true statement; right?
A. Yes, as far as I'm aware, that's true.
Q. Okay. That same bullet point says, "Promptly evaluate signs and symptoms of blood loss." Do you see that?
A. I do.
Q. And that's a reasonable piece of advice to give to a doctor; correct?
A. Yes.
Q. Now, because we've been talking about kidney function, I actually want to turn to the section of the labeling -- the sections on the labeling for Pradaxa that talk about kidney function issues. Okay?

A. Okay.
Q. All right. And before we get into that, there is a section on Page 2 of the label that talks about this dosing regimen for Pradaxa that the FDA approved; correct?
A. Yes.
Q. If you look up in Section 2.1 called "Recommended Dose," it says, "For patients with creatine clearance greater than 30 milliliters per minute the recommended dose of Pradaxa is 150 milligrams taken orally twice daily with or without food." Correct?
A. Yes, you read that correctly.
Q. And then the next sentence there refers to the patient population we've been discussing so much. "For patients with severe renal impairment creatinine clearance 15 to 30 milliliters per minute the recommended dose of Pradaxa is 75 milligrams twice daily." Correct?
A. Yes, that is stated.
Q. That was the recommended dose that the FDA came up with based on its modeling analysis; correct?
A. Yes.
Q. There's further down the page a section entitled "Dosing Adjustments." Do you see that?
A. I do.
Q. Okay. And do you see on the left-hand side there -- it's a little hard to see, but there's actually a line on

the left-hand side there. Do you see that?
A. Yes.
Q. And that's, that signals a change that's been made in the contents of a physician labeling; correct?
A. Yes. That links back to what you can find on the highlights as well. They tell you recent revisions and you can go there to see that.
Q. Okay. So that's a way to see how things have changed. And that section is entitled "Dosing Adjustments." Correct?
A. That's correct.
Q. All right. And just to talk about what doctors are told about patients and their kidney function, they're first told, "Assess renal function prior to initiation of treatment with Pradaxa." Correct?
A. Yes.
Q. And that's a reasonable warning; correct?
A. Well, this is not a warning. This is a, this is a different section. From a regulatory standpoint, "warning" has a very specific meaning.
Q. Fair enough. That's a reasonable piece of guidance to give to doctors; correct?
A. Yes, I would agree with that.
Q. And the reason that you want doctors to assess renal function is because they need to do that to determine which of those two doses of Pradaxa a patient should receive;

correct?
A. That should be what they're doing, yes, --
Q. Okay.
A. -- if they're doing this.
Q. And then the next piece of guidance given to doctors is, "Periodically assess renal function as clinically indicated, i.e. more frequently in clinical situations that may be associated with a decline in renal function and adjust therapy accordingly." Did I read that correctly?
A. You did.
Q. Okay. And when it says periodically assess renal function, that means check kidney function every once in a while as clinically indicated; in other words, as the circumstances of the patient dictate. Correct?
A. That's how I would define that, yes.
Q. Okay. That's a fair definition. And then in the parenthetical it actually says, "I.e.," or that is, "more frequently in clinical situations that may be associated with a decline in renal function and adjust therapy accordingly." Do you see that?
A. Yes.
Q. And so what the label tells doctors is after you've assessed renal function, you need to continue checking your patient's renal function; correct?
A. As needed.

Q. As needed?
A. Yes.
Q. Right? And then it goes on to say you should adjust therapy accordingly based on what you find when you check renal function; correct?
A. Yes.
Q. All right. And then the third piece of -- and do you agree that that's a reasonable piece of guidance to give to doctors?
A. Yes.
Q. Okay. The third piece of advice that the label gives to doctors in terms of how to treat their patients on Pradaxa is, "Discontinue Pradaxa in patients who develop acute renal failure while on Pradaxa and consider alternative anticoagulant therapy."
Did I read that correctly?
A. You did.
Q. And what that means is you might have to stop Pradaxa and put a patient on a different medicine if something happens with the patient's kidney function that makes Pradaxa inappropriate; correct?
A. It doesn't say it quite that way, but certainly that's what it's advising physicians to do.
Q. Is that a fair interpretation of what it says?
A. It could be.

Q. Okay. And would you agree with me that that is a reasonable -- that language that appears there that we've just talked through, that is a reasonable piece of guidance to give doctors about treating patients who are on Pradaxa?
A. Yes.
Q. Okay. Do you agree that in the circumstances -- in a circumstance like what's described there, the possible need to adjust the, the dosing of therapy, would you agree that reducing the dose of Pradaxa to 75-milligram in patients with serious kidney problems, that's a possible way to reduce exposure to Pradaxa in those patients?
A. It's possible, but without measuring, you don't know.
Q. Do you agree that reducing the dose of Pradaxa, going to a 75-milligram dose of the medicine in a patient who has severe kidney problems is a way to reduce the risk of bleed in a specific situation?
A. Could you state the first part of your sentence again?
Q. Sure. Reducing the dose of Pradaxa, that is, going to the 75 in a patient who has severe kidney problems, is a way to reduce the risk of bleed in a specific situation?
A. So that's what I believe we don't have data on. So I can't really answer that "yes" or "no."

MS. JONES: Your Honor, may I approach?

THE COURT: You may.

BY MS. JONES:

Q. Dr. Plunkett, do you recall giving sworn testimony in this matter in March of 2018?
A. Not this case, but a different case, yes, I did.
Q. Do you recall giving testimony --
A. Yes, I did.
Q. -- in a Pradaxa litigation? And I've handed you -- did I hand you a binder?
A. No, you didn't.
Q. I'm so sorry. I apologize.
A. That's okay.
Q. Dr. Plunkett, I have handed you a copy of your sworn testimony from March of this year. And I'm going to ask you to turn to the tab that reads March 1st, 2018, a.m.
A. I'm there, yes.
Q. Okay. And I'm going to ask you to go to Page 31, lines 4 to 8. Are you there, Doctor?
A. Yes.
Q. Okay. And do you recall that this was testimony that you gave under oath?
A. Yes, it is.
Q. Okay. And do you recall being asked at line 4, Page 31, "Reducing the dose of Pradaxa, going to the 75 in a patient who has severe kidney problems is a way to reduce the risk of bleed in a specific situation?"
Do you see that question?

A. I do.
Q. And do you see your answer where it says, "In this label specific for the issue of kidney function change, yes, that is true."
Was that your testimony?
A. It was.
Q. Okay. Dr. Plunkett, just continuing on this topic of kidney function and exposure, would you agree that the reason that doctors are told to test kidney function in patients on Pradaxa is because Pradaxa is cleared through the kidneys?
A. Yes.
Q. Okay. And that's sometimes referred to, you might see in the documents, renal clearance?
A. Yes. In my previous answer I said "yes" but the question you asked, it has to do with the extent of renal clearance. So you wouldn't necessarily have to do it if it wasn't totally clear, but that's the issue. It's almost all cleared that way.
Q. Okay. I understand your point. Because Pradaxa is a medicine that is significantly cleared through the kidneys, doctors are told that they need to evaluate a patient's kidney function; correct?
A. Yes, that's correct.
Q. And that's because in that circumstance given the

extent to which Pradaxa is cleared through the kidneys, there is a relationship between kidney function and exposure; correct?

A. Right. And it's really the only way it's cleared from the blood is through the kidneys.

Q. Okay. Do you agree with the statement that renal function is the main determinate of exposure in patients on Pradaxa?

A. The main determinate?

Q. Yes.

A. I have seen that statement by scientists, yes.

Q. Scientists at the FDA; correct?

A. Yes, I have seen that.

Q. Okay. Do you agree with that statement?

A. I think it's a significant contributor, but there are others that can be just as important. But certainly if you -- if everything else is equal, in other words, you don't have other drugs on board, things like that, yes, I absolutely think just someone with Pradaxa with or without kidney failure, yes, it's a main determinate.

Q. Okay. And do you specifically recall that statement appearing in the summary review for Pradaxa that was prepared by Dr. Unger?

A. Yeah. In fact, we may have read that yesterday.

Q. Yeah. And, actually, if you still have it, it's

Exhibit 5827. I can put it on the screen if it's going to require you to dig through your pile.

A. No. It's right here.

Q. Okay. Please put up 5827. I believe it's already admitted into evidence. And we're going to -- let's start with Page 1 just to refresh.

So again, Dr. Plunkett, this is a copy of the summary review by the FDA on Pradaxa in 2010 when it was considering the application for the medicine for atrial fibrillation; correct?

A. Yes.

Q. And then if you turn to Page 5 of the FDA summary review, you see that there is -- I'm looking for it on the page here. Down towards the bottom there's a section --

Actually, could we just call out the bottom half, Mr. Reynolds, just to see what it is?

So this is a section entitled "Pharmacokinetics." Correct?

A. Correct.

Q. And that's one of the topics you were talking with the jury yesterday; correct?

A. Yes.

Q. And if we go down to the third paragraph it says, "Dabigatran is mainly eliminated in the unchanged form via glomerular filtration, thus renal function is the main

determinate of exposure." Do you see that?

A. Yes.

Q. And it says mainly 80 to 85 percent eliminated through the kidneys; correct?

A. Yes.

Q. And that was the point that you made with Mr. Moskow yesterday; correct?

A. Yes, I believe we did.

Q. And they go on to say, "For that reason, renal function is the main determinate of exposure." Correct?

A. Yes, and my clarification which is all things being equal. But I would agree with the statement as they've written it.

Q. Okay. And you understand that Boehringer --

We can take that down. Thank you, Mr. Reynolds.

You understand that Boehringer warns in the labeling for Pradaxa that problems with kidney function, reduced kidney function could lead to increased anticoagulant activity; correct?

A. Yes, that's true.

Q. Okay.

A. If what you mean is by reducing exposure, yes.

Q. Yes. And by what I mean is if your kidney functions are getting, is getting worse, your exposure might be getting higher; right?

A. Right. So I would take it as increased anticoagulant activity if your exposure is getting higher. Maybe I just misheard you.

Q. No, I think we're using different terms for the same concept. Increased anticoagulant activity, I mean to say you have more of the medicine that you're being exposed to; correct?

A. That's correct.

Q. Okay.

MS. JONES: Your Honor, it's noon. This is probably a sensible breaking point.

THE COURT: All right. We'll take our lunch break now. Can you be back by 1:00? That's just a little short of an hour. Is that all right? I'm going to also advise you today we have to end at 4:00 today.

So with that, Dr. Plunkett, you can step down. Don't discuss your testimony.

Ladies and gentlemen, make sure you have your stickers and follow my other instructions on breaks. We'll see you back here at 1:00.

(Jury retired from the courtroom at 12:05 p.m.)

(Recess taken at 12:06 p.m.)

HUNTINGTON, WEST VIRGINIA

FRIDAY, OCTOBER 5, 2018, 1:01 P.M.

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(Jury not present.)

THE COURT: All right. Before we proceed, I would like to request of counsel that whenever you use a learned treatise, like the ones that you used today -- are you tendering those to the clerk?

MR. MOSKOW: I don't think it was our --

THE COURT: You don't need to. Okay.

THE CLERK: Well, they are on the exhibit lists.

THE COURT: Terry says some of them are listed on the exhibit lists, so --

MS. JONES: Well, we have marked them for identification purposes so that we can just keep track of what we used in that regard, but I don't think there was ever any intention they would be going back to the jury.

THE COURT: Okay. And our concern is to make sure that we don't get confused. So I guess if you're not physically tendering it to the clerk, we don't need to worry about it.

MR. MOSKOW: Your Honor, maybe I could suggest something that might be helpful to the clerk as well, which is that the parties have used specific codes to identify literature. So, for example, for the plaintiffs, anything

that begins from 3000 forward is a learned treatise and would not be a full exhibit, and I believe theirs is 5000.

MS. JONES: I think that's right.

THE COURT: Okay. Well, that may be helpful, but --

THE CLERK: But all of your exhibits are 5000 and above.

MR. MOSKOW: So if it starts with 3000, if it is in between 3000 and 3999, it's a plaintiffs' learned treatise. If it is between 5000 and 5999, it's a defendant's learned treatise.

THE COURT: Okay. Well, I'm fine as long as you're not confusing it with actual exhibits so we don't have to worry about keeping track physically up here.

Let's bring the jury back.

(Jury present.)

THE COURT: All right. We're ready to resume.

LAURA PLUNKET, Ph.D., PLAINTIFFS' WITNESS, PREVIOUSLY SWORN

MS. JONES: Good afternoon, Dr. Plunkett. And good afternoon, members of the jury.

CROSS-EXAMINATION (Continued)

BY MS. JONES:

Q. Dr. Plunkett, I wanted to turn back to Exhibit 5884, which is that version of the Pradaxa label from January 2012, if we could.

And I wanted to just have us wrap up our discussion of the

subject of renal function, and what the label says about renal function and its relationship to anticoagulant activity and exposure in Pradaxa.

Okay?

A. Okay.

Q. That long introduction.

You understand -- actually, let me ask you to just turn to page 2 of Exhibit 5884 in the label.

Do you see down at the bottom of the page, there is a section that is entitled Warnings and Precautions?

A. Yes.

Q. Okay. And the Warnings and Precautions section includes the key safety information about the medicine, correct?

A. Yes.

Q. All right. And the first section of Warnings and Precautions reads: Risk of bleeding. Pradaxa increases the risk of bleeding and can cause significant and sometimes fatal bleeding, correct?

A. Yes.

Q. And that's that same warning we saw in the highlight section, correct?

A. Yes.

Q. What I wanted to ask you about is actually on the next page, page 3 in that first warning section in the label for Pradaxa.

There is a section of the very top that reads: Risk factors for bleeding include the use of other drugs that increase the risk of bleeding, for example, antiplatelet agents, heparin, fibrinolytic therapy and chronic use of NSAIDs.

Did I read that correctly?

A. Yes.

Q. And that's just a reference to the idea that we were talking about earlier with the Med Guide, that if you are on Pradaxa and take certain medicines that increase the risk of bleeding, your risk of bleeding can go up even further, correct?

A. Yes.

Q. All right. And then the next point related to kidney function is in the further sentence that appears there.

Pradaxa's anticoagulant activity and half-life are increased in patients with renal impairment, correct?

A. Yes.

Q. And I think that's what we were talking about right before the lunch break, this idea that if patients have kidney problems, the anticoagulant activity of Pradaxa is higher, correct?

A. Yes.

Q. And on the other side of the coin, the half-life is increased. In other words, it takes longer for the body to

get rid of the medicine, correct?

A. Yes.

Q. And the label for Pradaxa specifically tells doctors about that, correct?

A. It is in this sentence, yes.

Q. Okay. And then the one other thing I wanted to hit on while we're in this section is actually in the next paragraph, so we don't have to flip back and forth too much.

Do you see the first sentence of the next paragraph in that warning?

A. Yes.

Q. What does it say?

A. A specific reversal agent for dabigatran is not available.

Q. So that warning about the absence of a reversal agent for Pradaxa is in the physician labeling for the medicine, correct?

A. Yes, but not in the Medication Guide.

Q. Okay. If we look further down to Section 5.3, there is an additional discussion of this idea of Pradaxa exposure.

Do you see that?

A. Yes.

Q. And it says in the second paragraph of that section: P-gp inhibition and impaired renal function are the major independent factors that relate in increased exposure to dabigatran.

Did I read that correctly?

A. You did.

Q. So what that means is, taking medicines that are P-gp inhibitors can increase your exposure to Pradaxa potentially, correct?

A. Yes.

Q. And, also, impaired renal function can increase your exposure to Pradaxa, correct?

A. Yes.

Q. That's in the labeling for the product, correct?

A. In the physician labeling here, yes.

Q. Okay. And then the next sentence says: Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

Did I read that correctly?

A. You did.

Q. And that tells doctors that if you have a patient on Pradaxa, who is also on a P-gp inhibitor and also has kidney problems, you can expect that patient's exposure to the medicine to increase even higher than it would if the patient just had one of those two conditions, right?

A. Yes. The physicians are being told this, yes.

Q. Okay. And then I just want to touch briefly again while we're in this section on the last paragraph of that second

warnings section in the Pradaxa label.

It says: Consider reducing the dose of Pradaxa to 75 milligrams twice daily when patients are on certain medicines and on Pradaxa, and they have moderate renal impairment.

You see that?

A. Yes.

Q. And then the last sentence says: Avoid use of Pradaxa and P-gp inhibitors in patients with severe renal impairment.

And that's the group of patients we've been talking about for now not quite a day, correct?

A. Well, we've been putting those -- I was talking about putting those two things together, yes.

Q. Okay. And so the physician labeling for Pradaxa tells doctors you might want to avoid using Pradaxa in patients who are on -- who are on a P-gp inhibitor and also have severe renal impairment, correct?

A. Yes, the physician labeling states that.

Q. And just to go back to this idea of anticoagulant activity. It's just basic pharmacology that the more of an anticoagulant that you have, the higher the risk of bleeding you have, correct?

A. I would argue that in this case it's not so much the increase in dose, but certainly with the issue of increase of exposure internally, yes, that's true.

Q. Okay. And I think, again, we're using slightly different

words to say basically the same thing.

This idea of exposure, not so much the number that is attached to the dose, correct?

A. That's correct.

Q. Okay. And you understand that Boehringer Ingelheim warns doctors that problems with kidney function could lead to increased exposure, correct?

A. In the physician labeling?

Q. Yes.

A. There is some discussion, yes.

Q. Okay. And increased exposure is just increased blood levels of the medicine, correct?

A. That's what I mean when I say it, yes.

Q. Okay. Understood.

I'm going to ask you to turn to page 6 of that same label, and there is a section entitled Pharmacokinetics.

Do you see that?

A. Yes.

Q. Okay. And about midway down the page, there is a section that specifically refers to renal impairment.

Do you see that?

A. I do.

Q. And those couple of -- those three sentences talk about, in the first sentence, that Phase 1 study that you were discussing yesterday, correct, that open parallel-group single

center study?
A. Yes.
Q. And then the second sentence says to doctors who are prescribing Pradaxa: Exposure to dabigatran increases with severity of renal function impairment, correct?
A. Yes.
Q. That means if you have problems with your kidneys, your exposure to the medicine will increase, correct?
A. Yes.
Q. Now, after that reference, there is a parenthetical to Table 3 in the label. Do you see that?
A. I do.
Q. And there's actually a table that appears immediately below that section on that heading for renal impairment.
A. Yes. Table 3, yes, I see it.
MS. JONES: Okay. I was just waiting on Mr. Reynolds --
THE WITNESS: Sorry.
MS. JONES: -- before I started talking about it.
Thank you, Mr. Reynolds.
Q. So Table 3 looks at -- let me describe it generally, and you can tell me if you think there are any tweaks you need to make to the description.
It generally describes exposure to Pradaxa for patients who have different degrees of renal impairment, correct? Or

renal function is probably a more precise way to say it because normal patients are there, too.

A. That is correct.

Q. Okay. And so they have at the top of the -- actually, if we look at the left-hand column, you see the heading for renal function, right?

A. Yes.

Q. And then you see there is a category for normal renal function, right?

A. Yes.

Q. There's a category for mild renal -- mild renal impairment, correct?

A. That's correct.

Q. There is a category for moderate renal impairment, correct?

A. Yes.

Q. And then there is a category for severe renal impairment, correct?

A. Yes.

Q. And that's the patient population that we've been talking about that is prescribed -- that is recommended the 75-milligram dose of Pradaxa in the labeling, correct?

A. Yes.

Q. All right. And next to the word severe, there is a little symbol of some kind. Do you see that?

A. Yes.
Q. And then there's a reference immediately under that table that tracks with that symbol. Do you see that?
A. I do.
Q. It says: Patients with severe renal impairment were not studied in RE-LY.
Did I read that correctly?
A. You did.
Q. That information is included in the doctor labeling for Pradaxa, correct?
A. In this section it is, yes.
Q. Okay. And it goes on to say: Dosing recommendations in subjects with severe renal impairment are based on pharmacokinetic modeling, correct?
A. It is stated, yes.
Q. And that first sentence is true, correct?
A. That is true.
Q. And the second sentence is also true, correct?
A. Yes, it is.
Q. All right. And if we look back up at that Table 3, the heading indicates that this table shows us the impact of problems with your kidneys on what is described here as dabigatran pharmacokinetics, correct?
A. Well, it -- yes. This is based on that Phase 1 data.
Q. Okay. And if you look down at the line for severe renally

impaired patients, you see that it reflects an increase of six times in the exposure or what's referred to there as the area under the curve, correct?

A. That's correct.

Q. And it also describes an increase in the half-life, the last column on the right, right?

A. Yes.

Q. And so what that tells doctors is, if your patient has severe renal impairment, that patient's exposure could be increased by six times.

That's reflected here, correct?

A. Yes. The AUC level, yes.

Q. It also tells doctors that it might take longer for the medicine to leave the patient's body, correct?

A. Yes.

Q. Okay. The other topic that you discussed a little with Mr. Moskow yesterday was the issue of gastrointestinal bleeding.

Do you remember that?

A. Yes, we talked about that.

MS. JONES: Can you take down that document, Mr. Reynolds?

I'm going to ask you to go to page 3 of the Pradaxa label that we've been looking at.

Q. And you understand that in this label there is specific

information provided to doctors about various types of bleeding events and how those bleeding events appeared in the RE-LY trial, in terms of how RE-LY -- how Pradaxa did versus warfarin.

Is that a fair description?

A. Yes, that's correct.

Q. Okay. And if we look at the heading of this section, you see that it's Section 6, Adverse Reactions.

Do you see that?

A. Yes.

Q. And then the balance of that page, the rest of that page really describes the experience with the medicine in the RE-LY study, correct?

A. That's correct.

Q. And then if you turn the page to page 4, you see that there is a reference there to the higher rate of gastrointestinal bleeding on Pradaxa versus patients on warfarin, correct?

A. Yes.

Q. And that second paragraph at the top of the page, it reads: There was a higher rate of major gastrointestinal bleeds in patients receiving Pradaxa 150 than in patients receiving warfarin. And then there's -- the statistics on that are included in the parentheses.

And then it goes on to say that there was also a higher

rate of any gastrointestinal bleeds, correct?
A. Yes.
Q. That information, some of which I think you talked about with Mr. Moskow yesterday, that 50-percent increased risk in GI bleeding, that is included in the physician labeling for Pradaxa, correct?
A. The issue of the 50-percent increase is here, yes.
Q. And that is a true statement, correct?
A. Yes. Based on the RE-LY data that I have seen, it is.
Q. Now, Dr. Plunkett, the label also includes information, as we've seen, about a class of medications known as P-gp inhibitors, correct?
A. Yes, another section in the label.
Q. Okay. One of the P-gp inhibitors that you described for the jury yesterday was something called Coreg or carvedilol, correct?
A. Yes.
Q. And as we saw earlier in the warnings -- we don't have to go back to them, but the warning section for Pradaxa specifically advises doctors that patients' exposure to Pradaxa might increase if they are also on a P-gp inhibitor, correct?
A. Yes. They're given, doctors are given that general information.
Q. And the labeling also warns, as we've already discussed,

or recommends that doctors might want to consider not prescribing Pradaxa to patients who have severe renal impairment and are also on a P-gp inhibitor, correct?

A. Yes. As a general statement, yes.

Q. And that statement in the labeling concerning P-gp inhibitors being a factor in increasing exposure to Pradaxa, that's a true statement, correct?

A. Yes.

Q. Now P-gp inhibitors, that's a class of medicines, correct?

A. It's a class descriptor, but it's not like when -- when you use the word class, as a pharmacologist, I think about drugs that are all within the same mechanism or use. So P-gp inhibitors include many different classes of drugs. But if you want to describe and talk about that characteristic, many classes of drugs have within them members that are P-gp inhibitors.

Q. And that's a helpful clarification.

So it's actually broader than a class of medicines that might be targeted towards treating a specific condition. P-gp inhibitors, as an umbrella term, can include lots of different groupings of types of medicines, correct?

A. Right. So it's important to know which type would go with the types of co-medication you might be using for the drug where you put it in the label.

Q. Okay. And so when you consider all those different

categories of types of medicines that fall under the P-gp inhibitor umbrella, there could be hundreds of those medicines, correct?

A. Not that are strong inhibitors --

Q. Okay.

A. -- which is the concern here.

But certainly, yes, there are -- I don't know that there's hundreds, but there are certainly dozens that --

Q. Dozens.

A. -- have some type of activity.

Q. Okay. And would you agree with the idea that not every P-gp inhibitor medicine affects Pradaxa exposure in the same way?

Let me ask a better question.

Would you agree that not every P-gp inhibitor medicine increases exposure to Pradaxa at the same level or to the same degree?

A. Can't answer that yes or no because it depends on some other qualifiers you'd have to put in that question.

Q. Okay.

A. For some -- for some of the drugs, I would be okay with that statement. For others, I think it depends -- there's dependence on how often it's given, ah, as compared to the timing of Pradaxa. There is a number of things that go into that.

Q. Understood.

So just to clarify on this point, if you turn to page 6 of Exhibit 5884 -- this is also in the pharmacokinetic section -- do you see at the bottom of the page there's a reference to drug interactions?

A. Yes.

Q. And do you see that P-gp inhibitors actually have their own -- their own section in that drug interaction section?

You see that?

A. I do here. In this label, they do.

Q. And they identify different P-gp inhibitor medicines in that section, correct?

A. Yes.

Q. And so, for example, if you look at the first medicine identified, dronedarone --

A. Well, there's -- the first sentence above has others. But I would agree the one set off by itself --

Q. Oh, thank you. Yes. I apologize, the italicized reference there.

It says: Exposure to dabigatran is 73- to 99-percent higher when it is administered with dronedarone than when it is administered alone.

Have I read that correctly?

A. You did.

Q. And then if you go to the next medicine, ketoconazole, the

systemic ketoconazole increased dabigatran area under the curve and Cmax values by 138 percent and 135 percent respectively, correct?

A. Yes.

Q. So you can see different data if you're trying to assess to what extent exposure might be increased by a P-gp inhibitor, correct?

A. I wouldn't say it quite that way.

I would say that it -- certainly if you don't monitor the same end points, you can get different numbers. That's part of what they're reporting here.

It's not clear that in dronedarone they are talking about AUC and Cmax separately. But I would agree if you're going to talk about them and compare them, it's always helpful to have the same end point you are looking at. But absolutely each drug could have some difference in the absolute number that you would calculate.

Q. Okay. And that was my question. I appreciate that.

And then if you turn to page 7 of Exhibit 5884 under that heading of P-gp inhibitors, there is a reference to clarithromycin. Do you see that?

A. Yes.

Q. And it says: Coadministered clarithromycin had no impact on the exposure to dabigatran, correct?

A. Yes, that's what it stated.

Q. Okay. Now, you discussed with the jury yesterday an article by the lead author named Wessler; is that right?
A. Yes, the P-gp paper.
Q. Yes. And I think it's in your binder at 3295 if you wouldn't mind getting to that one for me.
A. I'm there.
Q. Okay. I'm going to get to mine as well.
MS. JONES: I believe this has been admitted, so -- thank you, Mr. Reynolds.
Q. Again, Dr. Plunkett, this is a paper that was published on the P glycoprotein transport system and cardiovascular drugs, correct?
A. Yes.
Q. And in general, just generally speaking, what it does is it talks about the interactions between P-gp inhibitors, certain P-gp inhibitors and certain types of cardiovascular medicines, correct?
A. Yes.
Q. Okay. So the section of the article that you showed yesterday is on page 5.
A. Yes. Well, we actually went to page 4 on the table, but then also to page 5.
Q. Okay. Let's start with page 5 if we could, please.
A. Sure.
Q. Okay. And at the bottom of the page, you were talking

with Mr. Moskow about this sentence that begins on page 5 and carries over to page 6: Carvedilol inhibits P-gp activity to a similar degree as verapamil.

Do you see that?

A. Yes.

Q. And you were talking about that in the context of whether or not Coreg might increase exposure levels for patients who were on Pradaxa because Pradaxa had an interaction with verapamil, correct?

A. Yes.

Q. All right. But this -- this section of this paper is not actually talking about Pradaxa, correct?

A. This -- this paragraph?

Q. Yes.

A. No. It's talking about the beta blockers.

Q. Okay.

MS. JONES: So if we could call out that section on page 5, Mr. Reynolds, that includes that portion of the sentence. And if we could grab the last part, that is great.

Q. So this discussion that you showed to the jury yesterday, this is not talking about carvedilol inhibiting P-gp activity to a similar degree as verapamil in Pradaxa patients, correct? That's not what that says.

A. No. It's talking about carvedilol as its ability to inhibit P-gp like other beta blockers. And then the table on

the other page is where you get the comparison to verapamil.

Q. Well, if you read actually this whole sentence, it says: Carvedilol or Coreg inhibits P-gp activity to a similar degree as verapamil increasing serum digoxin levels up to 32 percent.

Do you see that?

A. Yes.

Q. So that's not -- that's not a discussion of how Coreg interacts with Pradaxa, correct?

A. Certainly they have not measured -- this sentence, this sentence or this paragraph doesn't have a study that it's pointing to with carvedilol and Pradaxa in the same sentence. Is that what you're asking me?

I would agree they're not reporting data on that specific interaction in this paragraph.

Q. And that is what I'm asking.

And I just wanted to clarify you weren't suggesting that that sentence would also apply equally to Pradaxa. You've not seen data to support that point with respect to Pradaxa, have you?

A. I disagree. With -- this information with the table on the page before, I am suggesting that carvedilol should pose the same, ah, potential interaction as verapamil does to Pradaxa. Unfortunately, the company has not studied those two, and that's why it's not in the label.

Q. Well, have you actually looked at the section in this

paper about Pradaxa?
A. Yes. It's in --
Q. It starts on page 4.
A. Yes, dabigatran. I think we also, I think, looked at this.
Q. Yeah, this was right under the table I think that you talked about with Mr. Moskow.
A. Yes.
MS. JONES: And if we could just grab that section at the bottom. This is a little bit of a puzzle exercise piecing this together.
Q. But you see that's the section, the beginning of the section on Pradaxa, correct, that reference to dabigatran?
A. Yes.
Q. And then if you carry over to the next page, that discussion of dabigatran and possible interactions with P-gp inhibitors continues, correct?
A. Yes.
Q. There is no mention in that section, yes or no, to an interaction with Coreg, correct?
A. There is no -- specific in this section, you're correct, because that data has not been collected.
MS. JONES: Okay. We can take that down. Thank you, Mr. Reynolds.
Q. Okay. Dr. Plunkett, I want to turn now to talking a

little bit about some of what you showed the jury in terms of labeling and company information outside of the United States.

Okay?

A. Sure.

Q. You talked yesterday about the company core data sheet, and you talked about the European label also known as the SMPC, correct?

A. Yes.

Q. And the SMPC in Europe is the doctor labeling in Europe, correct?

A. Yes.

Q. And if I understand your testimony correctly, you didn't do a comparison of the U.S. Medication Guide to the labeling for patients in Europe, correct?

A. That's correct. I did not go to find the -- the equivalent of the one in Europe for patients, that's true.

Q. Okay. So you were comparing what the company says about Pradaxa in the doctor labeling in Europe to the patient labeling in the United States, correct?

A. Yes.

Q. Now, there are differences -- without going into all the details of this, there are differences in the regulations for prescription medicines in Europe and the United States, correct?

A. There are.

Q. All right. And each of the regulatory agencies that are responsible for overseeing prescription medicines in those places, they can make their own decisions about medications, correct?

A. They can.

Q. Okay. And sometimes agents -- the FDA and its counterpart in Europe make different decisions, correct?

A. They can.

Q. And, for example, the 75-milligram dose of Pradaxa is not approved for stroke prevention in atrial fibrillation in Europe, correct?

A. That is true.

Q. All right. It's actually approved for the prevention of venous thromboembolic events in patients who have had certain types of surgery, correct?

A. That's correct.

Q. Now the FDA made a different decision and specifically approved that lower 75-milligram dose for atrial fibrillation patients with severe renal impairment in the U.S., correct?

A. They did.

Q. Okay. You understand that both the company core data sheet and the SMPC that you talked about with the jury yesterday, that those were submitted by the company to the Food and Drug Administration here in the United States.

You know that, right?

A. Yes, as part of their PSUR process.
Q. Okay. And you were anticipating my next question, which was they did that through a periodic reporting process that medicine companies have to participate in when they have prescription medicines that are regulated by the FDA, correct?
A. That's correct.
Q. All right. Did you look at all of the PSUR for Pradaxa over time to see what the company was giving to the FDA or wasn't giving to the FDA over time?
A. No, I didn't do a complete assessment. I've seen some, but I haven't done an assessment of every one.
Q. And you're aware that the PSURs that were submitted, for example, the company core data sheet to the FDA, those have also included descriptions of the company core data sheet and summaries of changes to the company core data sheet.
You know that, right?
A. Yes.
Q. All right. And so, for example, I'm going to ask you to look at a document we've marked as 9199.
(Counsel conferring.)
MS. JONES: May I approach, Your Honor?
THE COURT: You may.
MS. JONES: Dr. Plunkett, I've handed you what we've marked for identification as Defense Exhibit 9199.
Q. Have you ever seen this document before?

A. Yes. This is not the complete document, but certainly I have seen this complete document as well before.

Q. Well, you anticipated again my next question to you.

If you turn back to the second page of Exhibit 9199, you'll see that it's actually a document that is about 1,100 pages long.

Do you see that?

A. Yes, that's correct.

Q. In the interest of good order, we have not printed out all 1,100 pages. If there is something in my questions that necessitates seeing some other part, just let me know.

Okay?

A. Sure.

Q. All right.

MS. JONES: So, Your Honor, with your permission, we would move for the admission of Exhibit 9199.

MR. MOSKOW: Your Honor, as long as the record is clear that this is an excerpt from that exhibit, we have no objection.

THE COURT: It is now. It's admitted and may be published.

MS. JONES: Thank you, Your Honor.

MR. MOSKOW: Thank you, Your Honor.

(DEFENDANT'S EXHIBIT 9199 ADMITTED INTO EVIDENCE.)

MS. JONES: Thank you, Mr. Reynolds.

So, Dr. Plunkett, just to situate ourselves, you see up at the top the name of the document, a periodic safety update report.

Q. That's the type of reporting you were describing earlier, correct?

A. Yes.

Q. And then it describes the name of the product, which is Pradaxa, right?

A. Yes.

Q. And then it shows the PSUR period, and the date here is from September of 2009 to March of 2010.

Do you see that?

A. Yes.

Q. And so this was a period that was in the lead up to the approval of Pradaxa in the United States, correct?

A. Yes.

Q. All right. We're going to go to page 20 of this document.

Do you see there's a section there entitled Changes to the Reference Safety Information?

A. Yes.

Q. And do you understand that to be a reference to the company core data sheet?

A. Yes. It says that in this paragraph below.

Q. And as you rightly point out, it says: The reference safety information for this PSUR valid at data lock point DLP

of this PUR is the company core data sheet, and then it mentions the version there.

Do you see that?

A. Yes.

Q. And that's the company core data sheet version that you showed to the jury yesterday, correct, from December of 2009?

A. Yes. The December 10th version, yes.

Q. Okay. And if we just scroll down in this document, you can see here that there's a reference to the document being provided in Annex 1. Do you see that?

It's actually the next sentence right after what we just looked at, I apologize.

A. That's okay. I see it, yes.

Q. I may have led you astray.

And one of the things that the company mentions in the submission is a little further down: The following safety-related changes were made to the CCDS.

Do you see that?

A. I do.

Q. And one of the things that they flag is that there was an addition of new 150 milligram strength for the new indication prevention of stroke and systemic embolism in patients with atrial fibrillation, correct?

A. That's what it stated, yes.

Q. Okay. And so the annexes to the PSUR now are -- they are

hyperlinked, correct?

A. Yes, they are.

Q. So if someone wanted to find it easily, they could just click on a link in the electronic version, and it would take them to Annex 1, correct?

A. That's correct.

Q. Let's go to page 88 of this same document.

And on page 88, you can actually see that December 2009 company core data sheet that you were talking to the jury about yesterday, correct?

A. Yes.

Q. That was submitted to the FDA, correct?

A. Yes.

Q. Okay. And one of the things that I wanted to just ask you about is, the language in this version of the company core data sheet that you talked to the jury about, that information was submitted to the FDA even before Pradaxa was approved for the first time in the United States for atrial fibrillation, correct?

A. As part of this process, yes.

Q. Okay. And there were certainly discussions about the labeling for Pradaxa in that period leading up to the medicine's approval in October of 2010, correct, discussions with the FDA?

A. There were.

Q. Okay. And the FDA never told the company, based on your submission of the company core data sheet, we think you need to have some of this language in your label here in the United States.

Did you have ever see that in any of the documents you reviewed?

A. Ah, no. There -- what I saw was a response to the proposed labeling from the company, not this document.

Q. Okay. But my point is when the company submitted the company core data sheet, you've not seen anything to suggest that the FDA then said, well, we think you should take some of this language about, for example, excess of anticoagulant activity and put that in the U.S. label.

You've not seen any suggestion by the FDA on that, have you?

A. No, and I would be surprised if that process would happen.

Q. Now you also talked yesterday about the SMPC, the European label for Pradaxa, correct?

A. Yes.

Q. All right. And that was also something that was shared with the FDA, correct?

A. It was.

Q. Okay.

A. In this same process.

Q. Okay. Are you aware that there were also circumstances

where Michelle Kliewer, one of the regulatory leads at Boehringer Ingelheim on Pradaxa, shared a copy of the European label with Alison Blaus of the FDA?

A. I don't recall whether that was discussed in her deposition, so I'd have to review. I don't recall that.

Q. Okay.

MS. JONES: May I approach, Your Honor?

THE COURT: You may.

MS. JONES: Dr. Plunkett, I've handed you what we've marked as Defense Exhibit 5914 and Defense Exhibit 5915.

Q. Do you see that?

A. Yes, I do.

Q. Okay. And you've already told us that as part of its regular periodic reporting process with the FDA, that the company would have been submitting its SMPC to the FDA, correct?

A. Yes, and I've seen that done.

Q. Okay. And have you ever seen what we've marked as 5914 and 5915?

A. I've seen 5915 absolutely. That's the actual annex. I don't know about -- I don't recall this being discussed in her deposition, so I don't know.

Q. Okay.

MS. JONES: Your Honor, we would move for the admission of 5914 and 5915.

MR. MOSKOW: No objection.

THE COURT: It's admitted. You may publish.

(DEFENDANT'S EXHIBITS 5914 and 5915 ADMITTED INTO EVIDENCE.)

MS. JONES: Could we put up 5914 to start, Mr. Reynolds?

Q. Okay. And do you see here, Dr. Plunkett, that there is first an e-mail at the bottom from Lisa Matzen at BI to Michelle Kliewer at BI in September of 2012?

A. Yes.

Q. Do you see that?

Do you know who Lisa Matzen is at the company?

A. I don't know her personally, but I've seen her mentioned in e-mails before.

Q. You know she is one of the regulatory professionals for the company in Europe?

A. Yeah. She's a European person, yes.

Q. Okay. And then if we scroll -- what she says in her e-mail to Ms. Kliewer is: Dear, Michelle. As requested, the approved set of annexes covers all CCDS updates up to and including CCDS 07. A label change pertaining to CCDS 08 is under review.

Did I read that correctly?

A. You did.

Q. Then if we scroll up to the top of the e-mail, you can see

that Ms. Kliewer actually forwarded whatever Dr. Matzen sent to her to Alison Blaus at the FDA.

Do you see that?

A. I do.

Q. And the subject line is Pradaxa, current set of annexes?

Do you see that?

A. Yes.

Q. And do you see -- and this is something you can tell just by looking at those Bates numbers in the bottom right-hand corner.

Do you see that the attachment to that e-mail is 5915, that annex referred to in the e-mail exchange?

MS. JONES: Can we put up 5915, Mr. Reynolds?

THE WITNESS: If what you're asking me is that the Bateses run consecutively, yes. The bottom of 5914 ends in 153, and then 5915 ends in 154.

MS. JONES: Okay.

Q. And if we put up Exhibit 5915, we see that's a copy of what is referred to as annex, one of the annexes in the e-mail that we were just looking at?

A. Yes, that's correct.

Q. Okay. And that's a copy of the European label, the SMPC, correct?

A. That is correct, yes.

MS. JONES: We can take that down. Thank you,

Mr. Reynolds.

Q. Now, the SMPC is that document you showed that showed the table with the different risk factors for bleeding that were organized I think in two columns.

Do you remember that?

A. Yes. That's one of the things we showed.

Q. And then there was also that table that had the listing of the different coagulation assays, and then there was a reference to the dTT.

Do you remember that?

A. Yes. I believe we -- I believe we showed that, I don't recall. But I know it's in there, yes.

Q. Okay. Did you see, in reviewing any of the materials relating to the regulatory history of Pradaxa, that the FDA ever said, you know, we've looked at your European label, and we think you need to have some of that information in the label that you have here in the United States?

A. I have not seen that, no.

Q. And is it your understanding that actually some of the language that you have referenced in going through the SMPC and the CCDS, that some of that very language was proposed to the FDA, and the FDA rejected it for the U.S. label?

A. Yes. I think that was -- the jury should have seen some of that in the deposition, I believe, of Ms. Kliewer.

Q. Let me just talk about one example of that that is

relevant to what we've been talking about for the last day and a half or so.

You showed the jury the language from the CCDS and the SMPC that says Pradaxa is contraindicated in patients with severe renal impairment. Do you remember that?

A. Yes.

Q. And contraindicated means don't use it in these patients, right?

A. Yes. And I think I even described it as the risks would outweigh the benefits.

Q. Okay. Now do you know that Boehringer Ingelheim actually tried to get that language in the U.S. label for Pradaxa?

A. Yes, and I think we -- that was in another document earlier today.

MS. JONES: Your Honor, may I approach?

THE COURT: Yes.

MS. JONES: Dr. Plunkett, I've handed you what we've marked as Exhibits 5061 and 5062.

Q. Do you recognize those documents?

A. I'm not sure I've seen the e-mail, but I have seen, ah, the label.

Q. Okay.

MS. JONES: And so, Your Honor, we'd move for the admission of 5061 and 5062.

MR. MOSKOW: No objection.

THE COURT: They are each admitted.

(DEFENDANT'S EXHIBITS 5061 and 5062 ADMITTED INTO EVIDENCE.)

MS. JONES: Okay. Could you call up 5061 to situate ourselves, Mr. Reynolds? Thank you.

Q. So, Dr. Plunkett, you recognize that this appears to be an e-mail from Michelle Kliewer at BI in July of 2010, and she's sharing with some of her colleagues at the company a copy of what she refers to as the current USPI proposed to the FDA.

Do you see that?

A. Yes.

Q. Okay. And then if we can go to 5062, which is the attachment to that e-mail.

If you flip to the first page, you see that this is a red line document reflecting one of the earlier proposed labels by the company to the FDA, correct?

A. I am looking to see if there's red lines in here, but --

Q. Well, maybe they're blue lines. To be fair, they're probably -- I used red line as a general term, I apologize.

A. Okay.

Q. You see that there are just changes reflected in the document?

A. There are some, yes.

Q. Okay. I actually just want to focus your attention on page 2, and there is that section entitled Contraindications.

Do you see that?

A. Yes.

Q. Okay. And they are a list of different things where the company is proposing to say in the label this medicine shouldn't be used with this particular patient group.

Do you see that?

A. Yes.

MS. JONES: Could we go back to page 2, please? I think you had it initially. Yeah, that's perfect.

Q. And do you see that the second bullet listed there is severe renal impairment?

A. Yes, I see that.

Q. Okay. That was the company's proposal in terms of patients with severe renal impairment and Pradaxa, correct?

A. Yes, in this version of the label.

Q. Then if you go to page 4 of the label, there is a section at the top entitled Severe Renal Impairment, where it includes language very similar to the language that you pointed to in the CCDS and the SMPC, correct, on page 4?

A. Yes.

MS. JONES: Your Honor, may I approach?

THE COURT: Yes.

MS. JONES: Dr. Plunkett, I've handed you what we've marked as Defense Exhibits 5035 and 5036.

Q. Do you see those?

A. Yes.
Q. Do you recognize Exhibits 5035 and 5036?
A. Yes, I have seen both the e-mail and the label.
Q. Okay.
MS. JONES: Your Honor, we would move for the admission of 5035 and 5036.
MR. MOSKOW: No objection.
THE COURT: They are each admitted.
(DEFENDANT'S EXHIBITS 5035 and 5036 ADMITTED INTO EVIDENCE.)
MS. JONES: Okay. Let's start with 5035, if we could, and just look at how the FDA responded to the company's proposed labeling.
Q. You see this is an e-mail from Alison Blaus at the FDA to Michelle Kliewer at the company dated October 8th, 2010?
A. Yes.
Q. And in the e-mail she writes: Hi, Michelle. Please find the division's revisions to the dabigatran label. There have been a number of changes to every section. Some of the changes reflected are changes we made to our own language. Please accept all changes prior to making any of your own.
And then she says: I've inserted some comments for changes that we are requesting.
Do you see that?
A. I do.

Q. All right. And so this is the process that I think you described a little bit with the jury yesterday.

The company proposes a label. The FDA then has an opportunity to say here are some things we think should be different, correct?

A. Yeah. This is that negotiation I talked about.

Q. Okay. And then if you turn to Exhibit 5036, do you recognize that -- and this actually does have red lines -- the FDA's red line to the company's proposed labeling?

If you go to page 2 --

A. Yes.

Q. -- do you see that?

And if we go to the section we were just looking at entitled Contraindications, do you see that second bullet with that reference to severe renal impairment?

A. Yes.

Q. And what did the FDA do with that?

A. It has been struck.

Q. Okay. And then if we go to page 3 of that document in the core discussion section, there is the section entitled 2.5 Patients with Severe Renal Impairment.

Do you see that? It's about midway down the page.

A. Yes, I see that.

Q. And what the FDA did was they took out the contraindication, and they proposed instead that the

recommended dosage of Pradaxa in patients with severe renal impairment is 150 milligrams taken once every other day.

Do you see that?

A. Yes.

Q. And we now know that after some discussion and some analysis, they concluded that it would be the 75-milligram dose taken twice a day, correct?

A. Yes.

Q. So that language that you showed in the CCDS and the SMPC, that's language that the company proposed and the FDA literally struck from the label for Pradaxa, correct?

A. Yes. And they made a different proposal.

Q. Dr. Plunkett, we've talked a good bit about the FDA and its structure and the process for a medicine like Pradaxa, so I'm going to skip a lot of that discussion, but I did want to just ask you one question.

The company, as part of its development of Pradaxa, did both preclinical and clinical studies, correct?

A. Yes.

Q. And that means studies that involved humans and some that involved animals, correct?

A. Yes.

Q. All right. And Boehringer shared every one of those studies with the FDA, both the preclinical and the clinical studies, correct?

A. That's my understanding, yes.
Q. And when BI submitted Pradaxa for approval by the FDA, the FDA got all of the raw data from the RE-LY trial, correct?
A. Yes, they were given the raw data.
Q. Okay. And BI also submitted all of the PK data for Pradaxa that served as the basis for the RE-LY -- excuse me -- the Reilly exposure paper that you talked about yesterday, correct?
A. The raw data went in, yes, that is true.
Q. And also as part of that process, do you know that the company submitted analyses of its data from RE-LY to the FDA in something called a clinical overview document?
A. Yes, I'm aware of that document.
Q. And is that a document that you reviewed as part of your work in this case?
A. Yes, I have seen that document.
MS. JONES: May I approach, Your Honor?
THE COURT: Yes.
BY MS. JONES:
Q. Dr. Plunkett, do you recognize Exhibit 5084?
A. Yes, I do.
Q. Do you recognize that as the clinical overview document that we were just discussing a minute ago?
A. Yes. I think -- I assume this is what you were referring to, yes.

Q. Okay. And as far as you know, this was a document that the company would have submitted to the FDA as part of its new drug application for Pradaxa, correct?

A. Yes.

Q. Okay. And in the interest of time, we're not going to go through all of this document, but I did just want to ask you, can we agree that in the contents of this document, that the company provided the FDA with information on various patient characteristics that might affect exposure and a patient's risk of having a stroke or having a bleed while they were on Pradaxa?

A. Yes, that is true. That would be in here.

MS. JONES: Your Honor, we would move for the admission of 5081 -- I'm sorry.

MR. MOSKOW: No objection.

MS. JONES: I apologize, 5084. Thank you, Mr. Moskow.

THE COURT: It's admitted.

(DEFENDANT'S EXHIBIT 5084 ADMITTED INTO EVIDENCE.)

MS. JONES: And could we just publish that briefly for the jury?

THE COURT: Yes, you may.

BY MS. JONES:

Q. Dr. Plunkett, you see up at the top of that document, the reference to clinical overview?

A. Yes.

Q. And also the fact that this is a clinical overview about the drug substance dabigatran etexilate, also known as Pradaxa, correct?

A. Yes.

Q. And then if you look a little further down for the document title, it says: MAA NDA for the Prevention of Stroke, Non-CMS Systemic Embolism and Reduction of Vascular Mortality in Subjects with Non-valvular Atrial Fibrillation.

Do you see that?

A. I do.

Q. And that's just a long way of saying this is a medicine that is being proposed for patients who have atrial fibrillation and are at risk of stroke, correct?

A. Yes.

Q. Okay. And you see the date there of November 10th, 2009?

A. Yes.

Q. And then there it refers to there being about a hundred pages of information here. Do you see that?

A. Yes.

Q. And then if we just click into the second and the third pages of that document, you see that there are various categories of information on different topic that were provided to the FDA.

Do you see that?

A. I do.

Q. So there's an overview of clinical pharmacology, for example. Do you see that?
A. Yes.
Q. And there is a reference to the effect of renal insufficiency. Do you see that?
A. I do.
Q. There's a reference to the effect of gender, age and weight. Do you see that?
A. Yes.
Q. There's a reference to P glycoprotein inhibitors, those P-gp inhibitors we talked about earlier. Do you see that?
A. Yes. That's further down, yes.
Q. There's a reference slightly further down to exposure response in AF patients. Do you see that?
A. Yes.
Q. And that's that discussion we've been having about the relationship between exposure and stroke risk or bleeding risk, correct?
A. Yes. It's the pharmacokinetic data from the RE-LY trial.
Q. Okay. And the balance of this table of contents lists various tables and figures that appear in this document, correct?
A. Yes.
Q. Okay. Dr. Plunkett, I wanted to ask you one other question about the FDA's review of the Pradaxa application,

and then I'll move into my last, what will be my last topic with you.

Do you recall that when the FDA was reviewing the application for Pradaxa, that it expressed the view that in patients with atrial fibrillation, warfarin had been severely under-utilized?

A. I've seen that said by FDA. I don't know which document it was in, but I've seen that, that discussed.

Q. That was a view that the agency expressed, correct?

A. In some document. I don't remember where it is, but I have seen that, yes.

Q. Okay. And do you also recall the FDA saying that the reason for that was fear of bleeding, fluctuations in INR, the importance of diet and the need for monitoring?

A. I can't tell you that all four of those were stated, but I know that those are all four things that were discussed generally for that drug, so I would assume that those would be there.

Q. Okay. And do you also recall the FDA recognizing that patients' occasional reluctance to use warfarin meant that there might be more strokes and more disability resulting from strokes because those patients didn't want to take warfarin?

A. So I don't recall that exact language, no.

Q. Okay.

A. But I'm certainly -- if they're discussing these issues,

they may have talked about the importance of patients being treated with anticoagulants when they have AFib.

Q. Well, do you still have 5827 in your pile there? It's the summary review document by Dr. Unger.

A. Yes, I do.

MS. JONES: And this has been admitted already. May we publish it, Your Honor?

THE COURT: You may.

MS. JONES: We're just going to go quickly to page 15 of the summary review, Dr. Plunkett. And I just want to focus on a paragraph, the third paragraph of -- the third paragraph on the bottom of that page 15.

Q. Do you see that?

A. Yes.

Q. It says: We know that warfarin is severely under-utilized in the AF patient population at a cost of increased strokes and disability.

Do you see that?

A. I do.

Q. And so that's the FDA saying we know some patients aren't using warfarin, and the result is that there are more strokes and more resulting disability as a result, correct?

A. That is what he is stating --

Q. And then --

A. -- I agree.

Q. I apologize. I didn't mean to talk over you.

And then it goes on to say: Some part of the resistance is fear of bleeding. The other part is related to fluctuations in INR, importance of diet and the need for monitoring.

Did I read that correctly?

A. You did.

Q. That was a view held by the FDA expressed during its approval process for Pradaxa, correct?

A. I would agree this is in this memo, yes.

Q. Okay.

MS. JONES: We can take that down. Thank you, Mr. Reynolds.

Dr. Plunkett, the last topic I wanted to cover with you relates to this notion of blood monitoring and your opinion that patients on Pradaxa require blood monitoring.

Q. Now, just to be clear, are you offering the opinion that patients on Pradaxa require regular routine monitoring like patients on warfarin receive?

A. No, and hopefully that was very clear when I gave my opinions yesterday.

Q. Okay.

A. That is not what I'm talking about.

Q. Okay. Now, you understand that the RE-LY results were achieved without adjusting the Pradaxa dose based on the

results of blood monitoring, correct?
A. Yes, I am.
Q. Okay. And the FDA specifically determined at the time of approval that it did not believe that monitoring would necessary for either of the doses of Pradaxa, correct?
A. Are you asking me was that the FDA's decision? Yes, that was their decision at the end.
Q. Okay. Now, despite that decision the company, Boehringer Ingelheim, during the RE-LY study had gathered data on blood concentration levels during the course of the trial, correct?
A. Yes.
Q. They did that for roughly 10,000 patients?
A. Yes.
Q. All that data got submitted to the FDA, correct?
A. It did.
Q. And the FDA performed its own detailed analysis of that blood concentration data, correct?
A. They did their own analysis, yes.
Q. After the FDA approved Pradaxa without the need for blood monitoring, the company continued to address this question of whether Pradaxa should be prescribed to patients and whether there should be a requirement for blood monitoring, correct?
A. I don't think that's quite what they were studying. But certainly that you could answer that question based on what they were studying.

Q. Okay. But they were looking at whether or not there was some range that patients should be maintained within through some kind of monitoring, blood monitoring regimen.

Is that a fair way of describing it?

A. Yes. That's how the Reilly paper started out, that's correct.

Q. Okay. So the company looked at that specifically after the medicine was approved, correct?

A. Well, it wasn't a new study. But it analyzed the data it had, and that was where the -- the paper started, yes.

Q. Okay. And in doing that, the doctors and the scientists at Boehringer Ingelheim, they were asking themselves whether they could make the medicine even safer even though it had already been approved by the FDA without blood monitoring, correct?

A. I would agree that was the discussion within e-mails, absolutely, about making the drug safer, yes.

Q. Okay. And you showed the jury a handful of e-mails that were created during these discussions that were going on at the company.

You remember that from yesterday, I assume?

A. Yes.

Q. And those e-mails reflect back and forth among various people at the company about this issue of whether there was a therapeutic range and whether blood monitoring would make the

medicine safer, correct?

A. It was more on the issue of therapeutic range. But, yes, that certainly was the discussion, yes.

Q. Okay. And specifically with respect to the Reilly exposure response paper that you showed to the jury yesterday, they were -- there were a number of scientists at the company who did not think that the science supported a therapeutic range like the one that folks were discussing within Boehringer Ingelheim.

A. I don't think that I would state that as a yes or a no. It's a little more complex than that.

I would -- I agree there was a discussion about that general issue, yes.

Q. Okay. One of those people was Dr. Martina Brueckmann.

I think you showed an e-mail from her, correct?

A. Yes, we did.

Q. Okay. And you showed the jury an e-mail that she sent discussing a draft of the Reilly paper; is that right?

A. Yes.

Q. Okay. Now Dr. Brueckmann, she's a medical doctor, correct?

A. Yes.

Q. Who worked at the company?

A. Yes. In Germany, I believe, yes.

Q. She's not a marketing person, correct?

A. No. She doesn't work in the marketing department that I know of, but yes.

Q. Okay. And that's a better way of putting it than I put it.

Another e-mail you showed the jury was from someone named Jutta Heinrich Nols.

Do you remember that e-mail?

A. Yes.

Q. Okay. And you showed the jury an e-mail from Dr. Heinrich Nols where she talks about whether or not the company should want to publish Dr. Reilly's exposure response paper.

Do you remember that?

A. Yes, I do.

Q. Okay. And Dr. Heinrich Nols, she's also a medical doctor, correct?

A. Yes.

Q. She doesn't work in the marketing department, correct?

A. No, not that I know of.

Q. Okay. And she specifically mentioned in that e-mail that you showed the jury that she was not empowered to release or stop the publication of the paper.

You remember that. Yes?

A. Yes.

Q. Okay. Now, the person who had that power was Dr. Jeffrey Friedman.

You saw his testimony I guess the day before yesterday, correct?

A. Yes.

I think there were others that had that power, but certainly that was -- that was discussed in the back and forth with him to her. That is true.

Q. Okay. And did you read doctor -- you were here during the play of Dr. Friedman's testimony, correct?

A. Yes, I was.

Q. And do you recall what he said about what he did when he received that e-mail from Dr. Heinrich Nols about whether or not the company should publish Dr. Reilly's paper?

A. Yes, I have seen the testimony.

Q. Okay. And do you recall him saying that he picked up the phone, and he called her, and he told her that he thought that e-mail was inappropriate?

A. Yes.

Q. Do you remember that?

A. I have seen that part of his testimony, yes.

Q. Okay. And you understand that the Reilly paper was ultimately published, correct?

A. It was.

Q. Okay. And the findings of the company's work were reflected in the contents of that paper, correct?

A. Not all of the findings from the earlier versions, but

certainly they made -- they produced a final version that was put into the literature.

Q. Okay. And the conclusions of that paper were that there was no optimal therapeutic range that would apply for every patient, correct?

A. That was a sentence in their conclusions, yes.

Q. Okay. And the other conclusion in the paper was that renal function was a factor that was probably most strongly predictive of exposure.

Do you remember that?

A. I believe that was in there as well.

Q. Okay. And that's consistent actually with Dr. Unger, with what Dr. Unger said in the summary review memo for Pradaxa back in 2010, correct?

A. The issue of the renal function?

Q. Renal function being one of the main determinants of exposure.

A. Yes, he did discuss that.

Q. As part of your work in this case, you've not identified one number or one therapeutic range that applies for every Pradaxa patient.

I don't think I heard you testify to that yesterday; is that right?

A. I don't think yesterday I was asked that question about -- the way you've just asked it, no, I was not. So we did not

talk about that.

Q. Well, I'll ask you the question.

As part of your work in this case, have you identified a single number or a single therapeutic range that you believe applies to every patient who takes Pradaxa?

A. I think what I've testified -- I haven't said it quite that way. What I have said instead was that the Reilly paper identifies a therapeutic range that the data supports could be used and applied to patients taking Pradaxa.

And then there's discussions in the documents and the information I've seen that -- whether the top of the range should be 215 or 150 or 250. But certainly all of those discussions identify the fact that when your blood levels are getting above the 150 to 200 range, there is a significantly increased risk.

And I think that's consistent, I hope, with what I've said before.

Q. And the -- I'm sorry. Go ahead.

A. So anyways, I'm trying to be consistent with what I believe I have testified to.

Q. Okay. I appreciate that.

The folks at Boehringer Ingelheim, they've not been able to come up with one number for everyone, right?

A. I disagree with that. Based upon the initial drafts of the Reilly paper, they certainly had a range that they

identified as a therapeutic range. But certainly I would say to you, yes, there were different numbers described within different documents, yes.

Q. Do you still have a copy of your March 2018 testimony, that black binder?

A. Yes, I do. The Boone? Yes.

Q. This time I'm going to ask you to turn to the tab that ends with PM as opposed to AM.

A. On the 1st?

Q. Yes.

A. Okay.

Q. Are you there, Doctor?

A. I need to know what page. I'm sorry.

Q. Oh, I'm so sorry. I didn't give you a page.

Page 19.

A. Okay. I'm there, yes.

Q. Okay. And I guess just to give you some context, do you see, just kind of scanning pages 18 to 19, you're being asked about this idea of a therapeutic range and whether the FDA or folks at BI have identified a specific range?

A. I think I'm talking here about the sweet spot issue, but yes.

Q. Okay. So do you see on page 19 where you were specifically asked -- well, just to provide some context, there is a reference there to folks at the FDA talking about

the issue of therapeutic range?

MR. MOSKOW: I think we are looking at something different, counsel.

THE WITNESS: I'm sorry?

MR. MOSKOW: We may be looking at something different.

MS. JONES: They may be looking at something different.

MR. MOSKOW: 3/1 p.m.?

MS. JONES: Yes, 3/1 p.m.

MR. MOSKOW: Page 19?

THE WITNESS: I was looking at line 9.

MS. JONES: Oh, I see. Yes. Okay. I'm asking you to look at page 19, line 5. Do you see that?

And you were asked a question -- it's a little hard because the question is broken up a little bit.

You said: They have asked that question and tried to answer it.

And then you were asked: And had not been able to come up with one number for everyone, right?

Q. Do you see that question?

A. I do.

Q. And then the answer was -- this was your sworn testimony: They have not -- they have not put that in the label, that is true.

That was your answer, correct?

A. Yes, it's not been put in the label, that is true.
Q. Dr. Plunkett, in connection with that conclusion in the Reilly paper that there is no single plasma concentration range that provides optimal benefit risk for all patients, the authors of that paper included both folks who worked at Boehringer Ingelheim and also doctors and scientists who didn't work at the company, correct?
A. They were not employees of the company, but they were working for the company on behalf -- as clinical investigators.
Q. They were working as scientists on issues related to Pradaxa, correct?
A. Yes, they were clinical investigators in the RE-LY trial.
Q. Okay. Every one of the authors of that paper signed off on the ultimate conclusion that there is no single plasma concentration range that proves -- provides optimal benefit risk for all patients, correct?
A. And I don't know that I can say yes or no to that because I haven't seen documentation everyone actually signed. But certainly I would agree that the paper -- they were all authors on the final version that was published, so I would hope that they had agreed, yes.
Q. You've not seen anyone come forward among that group of authors on that paper and say this doesn't reflect my opinion, have you?

A. That's correct. Other than -- other than there are some e-mails that go back and forth about issues related to drafts of the paper. But I would agree, I have not seen anything since the paper was published that indicates somebody has come forward and said, no, change this.

Q. And you understand that the company made a point of sharing the Reilly paper with the Food and Drug Administration, correct?

A. Yes.

Q. Did you see anywhere in documents that you reviewed that the -- that the FDA ever said we think that this paper, this paper by Dr. Reilly and others, justifies changing the labeling for Pradaxa?

A. I've not seen those words, no.

Q. And you understand that the FDA has a process where if they think a company should have given them information under their rules and regulations, they can tell a company that, correct?

A. If you're asking about can they send a -- send a letter, an untitled letter to the company asking for information, yes.

Q. Something like that.

A. They can do that, yes.

Q. And you're also aware that the FDA can require and, if necessary, order labeling changes if the FDA becomes aware of any safety information that it believes should be included in

the labeling of a drug?

A. Certainly that is now possible, yes, they can require.

Q. And in fact, you said now, but the FDA has had that authority the whole time Pradaxa has been on the market, correct?

A. Yes, that is true.

Q. Okay. And the FDA has never done that with respect to blood monitoring for Pradaxa that you're aware of, correct?

A. I have not seen a document that shows that.

Q. Okay.

MS. JONES: Your Honor, if I could just have a moment. I think I'm --

THE COURT: All right.

MS. JONES: Let me just confer with counsel.

(Counsel conferring.)

MS. JONES: Dr. Plunkett, I thank you for your time.

Your Honor, I could just have a chance to move all of my stuff.

THE COURT: Yes. We're going to take a pretty quick recess, about five minutes, before there's any redirect.

(Recess taken from 2:14 to 2:20 p.m.)

(Jury present.)

THE COURT: All right. We're ready. Now plaintiffs' counsel may conduct redirect examination of the witness.

MR. MOSKOW: Thank you, Your Honor.

Good afternoon, everyone.

Good afternoon, Dr. Plunkett, Your Honor.

Your Honor, before I start, I'm going to be using the Elmo with documents that are already in evidence. Can I have permission to publish those documents that have already been entered?

THE COURT: Yes. If they're already admitted, feel free.

MR. MOSKOW: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. MOSKOW:

Q. You covered a lot of information with Attorney Jones over the last day and a half or so. Let me apologize in advance for the fact that I'm going to be jumping around to try to just touch on a few points. And what I thought I would do is put them into five categories so that you know where I'm going, Dr. Plunkett, and the jury can follow along as well.

So we're going to talk a little bit about the FDA. We're going to talk about the SMPC, the foreign label. We're going to look at some of the studies and the company documents that Ms. Jones showed you. We're going to look at the doctors' label. And then we're going to finish today by talking about the patient Medication Guide.

Okay?

A. Okay.

Q. All right. As we start talking about the FDA, can you tell the jury why it is that Boehringer paid the FDA $1,405,000 in 2010 at the time it was reviewing its application?

A. So there's a program called user fee program. And essentially people that are submitting applications for new prescription drugs in the U.S. pay a fee, and that essentially helps the FDA hire enough people in order to be able to review applications quickly.

The program was put into place because there was a problem identified that it was taking very long to get new drugs through the pipeline, so it needed more staff. So that is what this program does. Anyone who submits an application, large companies pay a large fee, smaller companies may pay something smaller, essentially depending on how complex the application is. But, yes, that's what that is.

So essentially there is people that are hired within the drug review program, ODE, Office of Drug Evaluation. Their salaries are being paid by the user fee program.

Q. So when Attorney Jones put those lists in front of you of all the people who were involved in reviewing the documents, how if at all were these individuals paid by BI?

A. So it wasn't a direct paycheck to them, but certainly Boehringer is paying fees into the FDA, and those -- many of

those people that are listed there are ones whose positions are supported by these user fees.

Q. Now lots of the questions you were asked yesterday and today had to do with what the FDA knew and what they did with that information.

Is that fair?

A. Yes.

Q. I want to ask you whether your opinions in this case about what Boehringer didn't do are based on what -- the FDA's knowledge or on Boehringer's knowledge.

A. My opinions are based on what the company knew and, based on the regulations, what the company's duty is based upon those regulations with that information.

Q. Can you please tell the jury whose obligation it is to ensure and to craft actually a label that is adequate and to ensure that it is accurate for the entire time the drug is on the market?

A. So that is -- the label is the property and is owned by the company. It's the company's job to make sure that all of the information that they're aware that impacts patient safety and -- and also efficacy of the drug, the way patients use the drug, that information is -- it's the duty of the company and the responsibility of the company to make sure that that information gets put in the labeling and passed on so that physicians understand the risks of the drug -- for example, in

this case that's what we're talking about, risk -- and then also making sure that patients are also aware of not only what the drug is used for, but also the risks that they are going to encounter when they use that drug.

Q. On cross-examination, you were shown this document, which is Exhibit 9199.

Do you see that?

A. Yes.

Q. Okay. And this was something called a periodic safety update report; is that right?

A. Yes.

Q. And you pointed out and Attorney Jones noted that it's actually -- if the entire document were here, it's 1,159 pages.

A. Yes.

Q. Based on your experience in working with the FDA, is it a constructive way to get information into the label to dump 1,159 pages of information on the FDA?

A. No. That's not -- not my experience how a company does it when they have information that, ah, they believe needs to go into the label.

Q. Can you talk to the jury a little bit about that?

What is your experience on how companies who have information that they want to get into the label actually go about doing that?

A. Well, it was done in one aspect -- I think we talked about that. One of the ways to do that is they can file -- actually go to the FDA and request a change. And so there was a -- I think there was a document we talked about called a CBE, changes being effective. And I believe even in Ms. Kliewer's deposition it discussed a change to the label that was put in about this issue of monitoring renal function.

So that's an example. The company sees it as an issue, they have data that identifies it as an issue, and the company went and asked that that information be put into the label, and they actually made the label change. So that's an example of what needs to be done and should be done when that kind of information is available.

Q. In fact, as part of the periodic safety update report, are there places where you could actually inform the FDA of important issues that you think need to be addressed?

A. Yes.

Q. And I'm on page 3 of this document, and let's see if -- there's a paragraph that specifically talks about particular safety issues and concerns being investigated?

A. That's correct. That's a way to highlight there.

Q. And can you just read what the overall findings of this document are?

A. There are no new findings concerning the safety of Pradaxa in this PSUR.

Q. Based on your experience in working with the FDA, would you expect there to be a careful review of 1,159 pages looking for information that should be added to the label when the company indicates that there is nothing new here?
A. It -- I would say that they probably would not unless there was already something going on in the agency that the company wasn't aware of. Otherwise, no.
Q. You were asked some questions yesterday afternoon about -- about testing. Do you recall that?
A. Yes.
Q. And you were asked specifically whether you were identifying a specific test that could be done, right?
A. Yes.
Q. And do you recall what your answer was?
A. Yes.
Q. What was that?
A. That you should measure the level of Pradaxa or actually dabigatran in the blood.
Q. Are you aware of whether that is possible in the United States?
A. Yes, and I tried to allude to that, you can do that. There are laboratories, Quest and LabCorp are two big nationwide labs that can actually do that.
Q. Okay. And there is something called hemoclot. Do you know what that is?

A. Yes.
Q. What is that?
A. That is a test that has been developed and is actually being used in Europe. So it is a diagnostic test that allows you to be able to measure the activity of dabigatran in the blood because you can calibrate it to the concentration of the drug.

So it's an indirect measure. You are not actually measuring in the way that I am talking about measuring the level. There is methods of analysis to actually detect the drug itself. This is instead detecting the anticoagulant effect. It is more like the INR type of test in that way. It's more direct.

But when you calibrate that test to the concentration of dabigatran, in Europe, that can be used to actually come up with an understanding of what the blood level of the drug is.
Q. Are you aware of whether or not that's an approved, an FDA-approved test in the United States?
A. It is not.
Q. Is it still available in certain laboratories in the United States?
A. Yes. That's another issue.
Q. Why is that?
A. Just because it's not approved by the FDA, it doesn't mean that there aren't laboratories that use that test. It can be

used.

The difference is, if you don't have it as an FDA-approved test, then in their labeling, they would not be able to mention that that's the recommended test.

Q. Are you aware of whether academic institutions like Emery or Stanford or other university centers in the United States, whether they actually use the hemoclot test?

A. Yes, there are a number of places. In fact, you even see it discussed sometimes in the literature about it being used.

Q. Now, with regard to Pradaxa in the United States, has Boehringer ever recommended that a non-FDA-approved test actually be used to look at patients?

A. So there is a -- yes. I believe the ECT test is not FDA approved, but it occurs.

Q. So let me show you page 2 of Exhibit 5884 that Attorney Jones was showing you a little while ago.

And specifically in -- this may be a little bit hard to read, but in Section 2.2, there is language that reads: Generally the extent of anticoagulation does not need to be assessed. When necessary, use aPTT or ECT.

Do you see that?

A. Yes.

Q. So what does that mean to you as a scientist, that there's a test that is not FDA approved, but it's in the label?

A. It just means this is a test that can be used. It

doesn't -- to me when you see this in the label, they're not saying it is FDA approved. It just means it's useful.

Q. Do you remember just a few moments ago you were shown Exhibit 5014, which is a clinical trial overview from 2009, November 2009?

A. Yes.

Q. And do you recall that you just talked about it generally, that it includes risk information about different patient characteristics or different things that people might have that would affect their risk of bleeding?

A. Yes.

Q. Okay. And does this clinical overview make any kind of summaries?

A. It has a summary, yes.

Q. If we could turn to page 94, please.

Are you there?

A. I am.

Q. Do you see this paragraph on 94: There may be subjects who have multiple risk factors for increased bleeding risk that together may substantially increase risk. Concomitant antiplatelet use, concomitant P-gp inhibitor use, age greater than 75 years, moderate renal dysfunction, previous GI bleeding, high CHADS2 scores greater than or equal to three, are all factors that may increase bleeding risk. While there may also be increased benefit in such subjects, the risk of

bleeding may potentially outweigh the risk of stroke.

Do you see that information?

A. I do.

Q. Is that information you agree with or disagree with?

A. I agree.

Q. Now I'm going to give you a hypothetical.

Based on information in Boehringer's own documents, if you have a female woman who was 84 years of age, who was on Plavix, who was taking Coreg, who had severe renal dysfunction, had a history of gastrointestinal -- or I'm sorry -- gastroesophageal reflux disease, is that information that might indicate that this is a person at an excessive risk of bleeding?

A. Yes. Based on all of the data and the information I've seen, I would agree.

Q. I'm trying to stay in the order that I set for myself, so let me -- I want to ask you very quickly about the SMPC.

All right?

A. Sure.

Q. And I apologize. If I'm moving quickly, please slow me down. All right?

A. I'm fine so far.

Q. On Exhibit 80, I want to show you information on page 6, if that's all right.

A. Okay.

Q. Those patient factors that were reflected in the clinical overview that we just looked at --

A. Yes.

Q. -- are more or less reflected in the European label, right?

A. That's correct.

Q. And these are all factors that do what?

A. These are all factors that put the patient at increased risk of bleeding.

Q. And in the European label, in the SMPC, doctors were told that when they have all these issues, what should they do?

A. Well, they need to consider changing the dose or another drug altogether.

Q. But how would they know whether somebody needs to change the dose or be on another drug altogether?

A. Oh, I'm sorry. Yes. They are told to actually look at the exposure or look at the chance that the patient has excessive activity of dabigatran in their blood.

Q. Now we're going to talk a lot about the patient Medication Guide, but let me just ask you simply, does BI ever tell U.S. doctors to do this?

A. No, they don't, and that's one of the things I've talked about that's important.

Q. And when you were showing the jury the information that you had identified in the European label, were you comparing

the European label to the Medication Guide?
A. Yes.
Q. And why is that? What is it about what the European label -- the information that is in the European label that speaks to BI's obligation to communicate things, to tell patients what is going on?
A. To me, the information that we went over in the European label, and also some of the CCDSs we went over, those issues are ones that tell you how to identify yourself as whether or not you're somebody who is going to be somebody that would be likely to experience this serious risk of bleeding.
Especially for patients that have, ah, experience with anticoagulants, maybe on warfarin before, understand bleeding is a risk. But there's a specific way to look at this particular drug differently based on some of the issues it has -- like I talked about bioavailability, interference with certain things -- that you can actually maybe prevent a bleed by understanding that these things apply to you.
Q. How, if at all, does the information that is in the European label tell you whether BI knows that these are issues that can be communicated to folks?
A. Because they're there. I mean, the things that are described there are ones that are indeed, ah, somewhat described in the physician label, but then it doesn't make it to the patient.

And to me the most important concepts are the issue that you could have too much exposure. There is a relationship between your exposure and your risk, that you are one out of five per chance that you could be the person that, oh, by the way has that risk. And so there is a reason to think you could prevent or reduce your risk by -- with this drug by understanding your risk factors.

Q. Why is it that you're so concerned about language concerning the level of Pradaxa in the blood be communicated to patients here in West Virginia?

A. Because they need to understand that there is -- there is -- there is information out there that will allow you to get that information, that test, and make that choice so the drug can be used more safely. It's a safer drug when you are able to identify people and identify whether or not they're people where they're outside the safe range of exposure. And so I just don't understand why it wouldn't be a good idea to make this a safer drug.

And being that here, the patient -- it's important that the patient be provided that information, it needs to be there, then. Too much Pradaxa equals risk, and there's a way to figure out if you have too much Pradaxa.

Q. We were just looking at the European label, and it had that specific language, excess dabigatran exposure and how to test for it.

Maybe I'm repeating myself, but how would you do that?

A. How would you test for it?

Q. Yeah.

A. You would take your blood sample, and you would test it for the concentration. If you're already being tested for kidney function, we talked about that, you could take that sample that you've already drawn and use part of that, and the doctor could send it off. But you could also prick your finger, get a blood sample, and that could be used as well.

Q. Gotcha.

All right. So we've talked a little bit about the FDA. We talked a little bit about the SMPC. If I had more initials, I'd use them. But I want to now look at a couple of documents and the studies that we talked about this morning.

All right?

A. Okay.

Q. Attorney Jones just asked you whether you had reviewed e-mails of company employees talking about the idea of a therapeutic range.

Do you recall that?

A. Yes.

Q. And, in fact, you showed the jury some of those yesterday?

A. Yes.

Q. And one of the documents you showed was Exhibit 5. It was an e-mail conversation between Dr. Reilly and Dr. Brueckmann.

Do you recall that?

A. Yes.

Q. And when Attorney Jones was asking you questions, she asked you whether you would agree that they were discussing, you know, science and different interpretations of the science, and you said you couldn't quite answer that question yes or no.

Is that fair?

A. Yes.

Q. Can you explain to the jury why that is?

A. Well, because if you -- if you read these e-mails, it's more than science that's being discussed. It's talking about the issue of, ah, the goal of the drug and the fact that marketing -- the marketing goal was to have a drug with no monitoring. So, as a result, that's the message that they're -- that they understand needs to be complied with.

Q. And is Exhibit 5, and particularly the e-mail at the bottom of the page from Dr. Reilly to Dr. Brueckmann, representative of that discussion?

A. Yes.

Q. And what is it about this particular e-mail that you want to point out to the jury as representative?

A. It's the idea that they understand that -- if you read it down here, they understand in the parentheses that dose adjustment will optimize therapy. But yet above that, you can

see that the issue is the conclusions are not the ones that are wished for by marketing.

So it's the idea of these scientists being well aware of the influence of that -- that component of the company at least here. And I'm not saying -- I'm not saying anything about motives. I'm just saying generally that this tells me as a scientist that there is more going into their decision process and their discussion than just whether or not there is good science.

Q. And, you know, you were asked also, you know, what it is that you were recommending in terms of testing blood levels for Pradaxa.

And this is an e-mail dated August 1, 2011. So it's more than seven years ago; is that right?

A. Yes.

Q. And could you read the second sentence of Dr. Brueckmann's e-mail?

A. Maybe one has to clearly differentiate between initial dose adjustment with the help of a target range and regular measurements, which are certainly not needed.

Q. How, if at all, is that point consistent or inconsistent with what you've been telling the jury yesterday and today?

A. It's consistent. I'm saying -- I'm not saying do like warfarin routine monitoring, and I believe Attorney Jones asked me that question. That's not my opinion.

My opinion is this is useful information about the target -- about this therapeutic range that can be used to know whether, when a patient starts on the drug, it's the right dose or even the right drug for that patient. And that decision can be made early on.

Q. But isn't she actually suggesting the same thing that you said to the jury?

A. Yes, she is. In fact, there's other e-mails where you can see that they're -- that the scientists here discussing these issues understand -- there was another one we read about when we have a competitive -- a competitor out there, this will be something that makes us better.

Q. Well --

A. So it's that process of understanding that this idea of the really good data set they actually have could be used by them to make this drug safer and better, and yet they're choosing not to do that.

Q. In fact, that e-mail that you are referring to is the one at the bottom?

A. Yes.

Q. Dr. Reilly said, I actually think that once we have a competitor out there that is as good as we are, we'll be looking for ways to make our drug even better?

A. That is exactly right.

Q. I want to just -- last thing on this e-mail, you indicated

that marketing was playing a role.

Can you read the sentence that begins on the fourth line to the end?

A. The time may be a bit too early to introduce a target plasma level range from a marketing point of view. But if this could clearly demonstrate that additional benefits are obtained, this may be a path forward to differentiate ourselves from competitors.

Q. How, if at all, does that fit into your opinions that Boehringer knew there was a way to make the drug safer, but hasn't communicated that to patients here in West Virginia?

A. I think it's exactly on point with what I've been saying. The company obviously understands they have a way to make the drug safer. There's information and data their scientists are discussing. But instead of doing that, they're making no change, and that information isn't getting to the patients who I believe would like to have that. I would.

Q. I'm not sure this fits into any of those categories, but somebody left a note on my stack, so now I have to ask another question, which is, has any plaintiff or plaintiffs lawyer asked you to work on a project that you turned down?

A. Yes.

Q. Why?

A. Because -- so when I do this work, I do it because I believe in what I'm doing. Before I even agree to take a

case, I spend a couple of hours of my own time, not charged to the attorney, where I look at the issues, the science, and I see whether or not what they have told me they're trying to do is going to be something that I could support.

So there are cases that I turn down because I don't think the science supports it or just, in general, I just think there is something wrong with the approach that is being taken as far as trying to link it with cause and effect. Sometimes I don't believe there's a causal link there that could be identified. So depending on what I'm doing, I do turn down cases.

Q. So when you're asked have you ever testified in a product liability case whether the drug company was adequate, would there ever be a way you could do that?

A. Probably not unless I was approached by a defendant for one of these cases, and unfortunately I have not.

Q. If somebody did approach you, and you agreed with their position?

A. Yes, absolutely.

When I was at ENVIRON in the old days, when I worked for another consulting company, I worked on defense litigation, and they were cases that I believed had scientific support based on the information I had.

Q. All right. I want to now look at some studies very quickly if we can. The first one I wanted to ask you about is

Exhibit 6038, which is the Hariharan paper that you were asked about today.

A. Yes.

Q. And I hope you can remember your train of thought, but you were asked a question about this paragraph on the bottom of page 3. And you said you wanted to explain the idea of what the FDA's guidance -- the role that it plays in this area.

Are you able to remember what you were thinking?

A. I think so, yes.

Q. And what is that?

A. So if you actually read the guidance document, it talks about the fact that there are times when you can't ethically collect, for example, or just based on the way the study is designed, you can't collect data in all populations. And specifically in renal impairment, sometimes that is difficult. So what the guidance document says is here's the things that you need to consider if you're going to use this modeling in order to go forward with choosing a dose.

And if you actually read that document, when I read it, there is some information there that indicates that additional data still needs to be collected, and that's the issue. That's my -- when I talk about not being tested, the issue is testing the drug afterwards for more pharmacokinetic measurements is not saying it is testing the drug to see -- when you know pharmacokinetics or the blood levels or that

exposure predicts outcome, we know that there's a relationship between too much Pradaxa and risk of bleeding, that is the data that hasn't been collected in a controlled manner.

There has been observational -- she brought up some -- I mentioned that was an epidemiological study. I think I threw that out once, which I don't think we then explained.

But essentially there is different kinds of studies, the studies that are used for drug approval purposes by the FDA, and companies have controls built around them so that we know exactly who we're studying and what outcomes we're going to look for, so you know what people are exposed to, when they got the drug.

The problem with the observational work is you don't even know -- you can't control exactly when the people took their drug, what they took, how it was done. So as a result, there is limitations on that data, to me, as far as saying that that shows that this drug is safe and effective, that data doesn't show the drug is safe and effective. It adds to a weight of the evidence that you can collect, and all of those studies together may let you determine that it appears to be safe. But it's not the same as doing a study to show that 75 milligrams and severe renal impairment prospectively is indeed going to -- going to -- going to be as safe as it was shown -- as the 150 dose was shown to be in RE-LY.

Q. So the RE-LY trial is something called a controlled

clinical trial?
A. Yes.
Q. And that's the best thing that you can do in order to see whether a drug is safe and effective?
A. Well, that's part of drug approval, yes. It is the -- it's the type of study that has the most controls that FDA and the regulatory agencies define as the type of study you need to do to prove safety and efficacy. Less chance, less likelihood that what you get at the end is not really true.
Q. So if we are looking at papers that are based on insurance databases or Medicare, Medicaid databases, can you explain to the jury how that is different than an actual trial?
A. It's because of the fact that the people that are in them, that you didn't select them necessarily to be in a study for a particular purpose. Instead you gather the database, and you find the people that were on a drug, and then you look at when they started it and when they stopped it or are they still on it and determine did they report an event. So it just doesn't have the same level of control and understanding of the patient population.
Given that this is a patient population that we expect, first off, to be very variable -- severe renal people, when you looked at their data, blood levels were really all over the map -- being that we know that these severely renally impaired patients are on different drugs at the same time, all

of that isn't accounted for in those observational studies.

So we really don't know exactly were they really truly severely renally impaired? In fact, one of the studies indicates 93 percent of the people they studied, they didn't know if they were.

Q. We're going to talk about that in a moment.

A. So --

Q. Thank you.

Let me move you to Exhibit 9328. This was shown to you earlier today. Or it might have even been yesterday, I've lost track.

But this was part of the approval of the 75-milligram dose. Do you recall that?

A. Yes.

Q. Well, let me -- as long as we're here.

There was a statement that said: For the RE-LY study, the decision to not include or discontinue subjects with markedly decreased renal function was probably a rational decision. Dabigatran and its metabolites are renally excreted. Allowing patients with marginal renal function to enroll or continue in the study would risk the problem of generating excessive concentrations in these patients and risking additional bleeding.

Do you agree with that statement?

A. Yes.

Q. Why?

A. Because that's just the point. If you -- if you don't really know what their exposure is, we know that they're at risk, and that's the issue.

So, yeah, in these studies -- in a study like that or any study you design, you would need to be measuring blood levels as well as looking at outcomes, because that is the only way you know that people are also being protected when they are in the study.

Q. Okay. I want to turn your attention to the last page of Exhibit 9328, page 6, and I want to show you something that counsel didn't show you yesterday when she showed you this document.

And it reads: Since there is no empirical data on this population with regard to bleeding risk, particular attention post-marketing should be paid to bleeding and other safety events in those treated with the 75-milligram BID regimen and patients with severe renal impairment.

Can you explain to the jury why that is important information?

A. It's important -- I mean, I think that's a little more complex. You wouldn't want to put that on the Medication Guide just like that, but essentially this is the issue that I was talking about.

It's important to understand that all -- that what was

done to make a decision for this dose was computer modeling. They didn't actually have data to show that these people with certain levels of exposure had a decreased or an increased risk of bleeding. They weren't monitoring that. So they can't say that the drug, ah, has the same bleeding risk really with data as it does with the 150. They're assuming it does based on the modeling, but they didn't actually collect the data.

So I understand that in the physician labeling in one section there's a statement for the physician, but that's not the same as telling very directly that -- to the patient that this drug has not been tested in people like you, and we don't really know exactly what your risks are as far as when you reach an increased risk of bleeding.

I would argue if they said but we could monitor your exposure and mitigate that risk, that would be something that would be useful to the patient.

Q. Okay. I just want to touch on that last part you said.

A. Okay.

Q. If we could monitor exposure and mitigate that risk, that would be useful information, tell the jury what exactly you're proposing.

A. I'm proposing to tell the patient that if you are one of these people that are at severe renal impairment where we don't actually have the data, that monitoring the level of

Pradaxa in your blood when you start therapy will tell us whether or not you are one of those people that we should really be concerned about as far as being at an increased risk.

Q. One of the papers you were shown this morning, Exhibit 5747, was one of these prospective studies that you talked about?

A. Yes.

Q. Okay. And I think this one talks about the fact that it -- well, let me take a step back.

This paper was published in 2015. Do you see that on the bottom of the first page?

A. Yes.

Q. You would agree with me that 2015 is after September of 2013?

A. Yes. It's well after, yes.

Q. All right. And in this particular group, do you recall that there weren't a sufficient number of people on the 150-milligram dose -- I mean, excuse me -- on the 75-milligram dose for the company to actually make any conclusions about the 75-milligram dose?

A. That's correct. This was not a study directed at 75. They tried to see how many were there, but there weren't enough in order for them to draw any conclusions separately about whether the 75 was safe and effective.

Q. As a scientist talking to the jury about the 75-milligram dose, can you explain to them why this paper is helpful at all to their deliberation as to whether BI breached its duties to the Knight family?

A. Well, I don't think the paper is helpful at all if you're trying to determine whether or not the company had appropriately tested 75 or had given any information to the doctor even in the label about that issue. This is -- this data does not help in that regard.

Q. Do you recall being shown Exhibit 9327? This is a paper entitled Comparing Stroke and Bleeding Risk with Rivaroxaban and Dabigatran in Atrial Fibrillation, Analysis of the U.S. Medicare Part D Data.

A. Yes.

Q. Okay. Is this one of those observational studies that you were talking about?

A. Yes.

Q. And was this one -- you used the word controlled. Let me see if I can say it differently.

Did this one make sure that the people who were in the study and on the 75-milligram dose were the people who were supposed to be on that dose?

A. Yes.

Q. Could I turn you to page 7 of this paper.

Do you see there's a paragraph that reads: Although low

dose dabigatran and rivaroxaban are only indicated in patients with AF with reduced kidney function, only 52.6 percent of the patients receiving dabigatran 75 milligram had a diagnosis of chronic kidney disease?

A. That's correct. That was the point I was making. I think the other paper had 93 where they didn't even have data to tell them that, but that's the issue.

In many of these observational studies, that's the problem they have. If they did collect data on 75, they don't know that those were the -- those people were even supposed to be on 75 from the start.

Q. Do you recall -- this is the Hernandez paper.

Do you recall whether the authors in the Hernandez paper speculated as to why they had so many people on the 75-milligram dose as opposed to the 150-milligram dose?

A. Yeah, there is something later on in the paper, I believe.

Q. Let's take a quick look at that.

Do you see it says here: Although our study did not specifically examine the off-label use of the low dose dabigatran and rivaroxaban, we hypothesize that these low doses of anticoagulants were prescribed off-labelly in 2011 to 2013 for patients with normal kidney function who did have other risk factors for bleeding, such as hypertension or a history of stroke or bleeding.

Do you see that?

A. Yes.
Q. What does that mean?
A. Okay. So off-label means in the -- means it's not something that the drug was approved -- was actually approved for.

So the label use is use in patients with AFib, and the label use of the 75 would be in patients with severe renal impairment, where their kidneys just aren't working hardly at all. Off-label would be using 75 in somebody who didn't fit creatinine clearance less than 30, but they had better kidney function.

So that is what we're talking about, use in patients that the 75 dose wasn't even modeled to really fit. It was modeled to fit severe renal impairment. It wasn't modeled for these other issues. So we really have no information.

Q. How, if at all, does this paper help the jury evaluate whether BI breached its duties to the Knight family with regard to the 75-milligram dose?
A. I don't think it helps you at all make a decision on whether they did or they didn't.
Q. Are you aware of any real world studies where they controlled for issues of severe renal impairment to make sure that the people who were on the 75-milligram dose were -- actually had severe renal problems, severe kidney problems?
A. Maybe one.

Q. What --

A. Only one, though, but it's not -- it's not a real study. There's an observational study only.

Q. And are you aware of any, quote/unquote, real world studies of dabigatran that occurred prior to November of 2011?

A. No, not.

Q. I want to show you another one of the papers you were shown. It's Exhibit 5526, and it's entitled Stroke, Bleeding and Mortality Risks in Elderly Medicare Beneficiaries Treated with Dabigatran or Rivaroxaban for Non-valvular Atrial Fibrillation.

Do you remember this one?

A. Yes, I do.

Q. And we haven't really talked about this, but on the front page of most of these articles there's like a little summary section that has important information, right?

Every one of the papers we have looked at, they have something -- what's that called?

A. The abstract.

Q. The abstract.

And what's the purpose of the abstract?

A. It's to summarize right up front the most important findings and also the design of the study.

So a scientist will read the abstract first, and then they will decide whether or not the study has anything that might

be useful to them, and they will delve in further. So the conclusions and the ultimate design are usually put up front.

Q. Can you tell the jury what drug was actually studied in this -- in this paper?

A. Well, I guess you mean the dose.

Q. Yeah.

A. It's 150 milligrams of dabigatran is what they drew conclusions on.

Q. Is this paper either designed or representing to the public that it has providing valuable information about the 75-milligram dose?

A. No. And like the other ones we've discussed, this paper suffers from those limitations of not knowing if people that were on 75 were the people that were supposed to be on 75.

Q. What help do you believe this paper is to the jury in determining whether or not Boehringer breached its duties to the Knight family?

A. Again, I don't think these papers provide that evidence for the kinds of things that I've been talking about. In other words, they don't provide that anything was actually studied -- studied in a way that would be able to show that the drug was actually safe and effective as used in patients with severe renal impairment.

Q. Okay. One of the documents that you were shown today is Exhibit 9194. It was a clinical trial report from 2014.

Do you recall that?

A. Yes.

Q. All right. So 2014 is after September of 2013?

A. That's correct.

Q. Okay. And with regard to this particular study, you had indicated that you had concerns when you were being asked questions about it, and they specifically had to do types of patients that were enrolled.

Do you recall that?

A. Yes.

Q. Can you explain to the jury what your concerns were about that?

A. So this paper was a paper that wasn't being -- people didn't have AFib, so even -- and it was also short term, only for seven days. So different patients, short term isn't going to tell us what we need to know about the chronic use in AFib patients of 75 milligrams in patients with severe renal impairment.

Q. Is that important?

A. Yes. Because that's the type of data that you would typically collect if you were going to actually prove that this -- this drug had those benefits.

Q. Does this paper or clinical trial overview, to the extent that you reviewed it, reflect outcome data?

A. No.

Q. What is outcome data?

A. So outcome data in RE-LY, for example in RE-LY, is did somebody have a bleed? Did somebody have a stroke? That's the outcome of taking the drug. Did we prevent a stroke? Did somebody bleed? This is a pharmacokinetic study, so it is looking at this issue of how much Pradaxa did they measure in their blood.

Q. How long was this study?

A. Seven days.

Q. Seven days in 16 people?

A. Yes. Small study and for a short period of time.

Q. Is this a comparison of the 75-milligram dose to people on warfarin?

A. No.

Q. You were also shown Exhibit 9191. Do you recall that?

It was a clinical trial report with regard to another study that was done in two thousand -- well, it was actually published in May 2016.

Do you see that?

A. Yes.

Q. When I say published, have you ever seen this paper in the medical literature?

A. No, I've not seen this one. But the study report was -- was made available in 2016.

Q. Okay. This one -- and certainly May of 2016 is after

September of 2013?

A. Yes.

Q. I don't want to spend a lot of time on this paper, but I want to go to conclusions at the front here.

And I drew on mine while Attorney Jones was talking to you about it, so I apologize if it's hard to read.

Can you read the first paragraph of the conclusion?

A. Sure.

The observed dabigatran plasma concentrations in patients with severe renal impairment following 75 milligrams dabigatran etexilate, in parentheses Pradaxa, twice daily, were generally in agreement with those predicted by models developed from data in previous trials, although with a tendency towards under prediction of median and higher concentrations.

Q. Can you tell the jury as a scientist how something can be consistent with a model when the finding is that it under predicted the median and high concentrations?

A. Well, you can say it's consistent depending on what you compare. But I would say this is telling me it's not entirely consistent, that there are issues with -- with the model.

Q. So in their internal document talking about the study, they make a finding that it under predicts median and higher concentration.

What does that mean for people with really bad kidneys?

A. So that's what you're worried about, is those higher concentrations, because they are not going to let the drug out. So if you're under predicting with that model, then you're not getting an understanding of what actually people have in their blood is what they're saying.

MR. MOSKOW: All right. I'm going to try to move on here and try to talk about the doctors' label very quickly.

Permission to approach, Your Honor?

THE COURT: Yes.

MR. MOSKOW: Doctor, I've handed you what's been marked as Exhibit 86 for identification.

Q. Are you able to identify what this is?

A. Yes.

Q. What is it?

A. This is the launch label, the first label for Pradaxa that -- when it was approved.

Q. Is it the launch label or do you see the revised date?

A. Oh, I'm sorry. I saw up here. You're right, revised in 2011.

Q. Okay.

MR. MOSKOW: Your Honor, I'd offer 86 as a full exhibit.

MS. JONES: No objection.

THE COURT: It's admitted and may be published.

MR. MOSKOW: Thank you, Your Honor.

(PLAINTIFFS' EXHIBIT 86 ADMITTED INTO EVIDENCE.)

MR. MOSKOW: In particular, I don't want to spend a lot of time on this, but you were shown language from a different label on direct examination that -- excuse me -- on cross-examination where Boehringer was telling physicians about severe renal impairment.

Q. Do you recall that?

A. Yes.

Q. In fact, the exhibit you were shown was Exhibit 5884. And the part of the -- and, again, I apologize for my messy highlighting.

The part of the label that you were shown with regard to this was on page 6, and it had to do with Table 3 and language underneath that that said -- well, first of all, the table identified severe renal impairment, right?

A. Yes.

Q. So really bad kidney problems.

And then underneath it, it said: Patients with severe renal impairment were not studied in RE-LY. Dosing recommendations in subjects with severe renal impairment are based on pharmacodynamic modeling.

Do you see that?

A. Yes.

Q. And that was information that you said that you were aware of?

A. Yes.
Q. Okay. I want to go to back to Exhibit 86, and I want to look at page 5. I'm going to try to do these side by side, but I probably won't do it very well. So let me -- I guess that's close enough.
Are you able to see Exhibit 86?
A. I have both in front of me, so I'm good.
Q. Can you tell the jury where in Table 3 in Exhibit 86 it reflects severe renal impairment?
A. It doesn't. This part of the label is different in this -- in the 2011 label versus the label we looked at.
Q. Okay. Now, I know you're not familiar with the facts of Mrs. Knight's Pradaxa use, but let me ask you this.
If you had a patient who started on Pradaxa when Exhibit 86 was the operative label, what information would be available to the doctor?
A. There would -- nothing in this section on severe renal impairment and certainly wouldn't have the other statement which you pointed to. They wouldn't know about that, about the fact that patients were not studied.
Q. Can you tell the jury if Boehringer Ingelheim sent a dear doctor letter that we talked about yesterday, did they send any kind of communications to doctors in the United States telling them that they had added information into the label about severe renal impairment?

A. I actually asked if that had happened, and I was -- I'm not aware that they actually sent such a letter. I haven't seen one.

Q. And were you aware of whether they ever sent any kind of letter to doctors or anyone indicating they had added a statement that the data had never been tested in real people?

A. The same answer, I'm not aware of that having happened.

Q. You were asked a lot of questions about the doctor's label yesterday and today.

Do you recall that?

A. Yes.

Q. And I want you to tell the jury -- well, let me take a step back.

Based on your work as a consultant working with pharmaceutical companies over the last 30 years or so, what is your understanding of whether in West Virginia a company should warn the patient or warn the doctor?

MS. JONES: Your Honor, may we approach briefly on this?

THE COURT: You may.

(Bench conference, reported.)

MS. JONES: I object to this. The jury will be instructed on West Virginia law. Dr. Plunkett is not a West Virginia legal expert. I think the question is inappropriate.

MR. MOSKOW: Her opinions are informed by the opinion

of who it has to go to.

THE COURT: Well, I think if you rephrase it, you can ask it.

MR. MOSKOW: Okay. I'll rephrase it.

THE COURT: Okay. How do you intend to rephrase it?

MS. JONES: No, Neal, he wants to know how you are going to rephrase it.

MR. MOSKOW: I will rephrase the question, and it will be something to effect of, now, Doctor, in reaching your opinions in this case, did you have an understanding as to who the warning should go to?

THE COURT: I think that's fair enough.

MS. JONES: I still think that speaks to a legal issue. I mean --

THE COURT: It has an implication for the legal issue, but it's -- I will permit that.

MS. JONES: Okay. Thank you, Judge.

(Bench conference, concluded.)

THE COURT: All right. Rephrase your question.

MR. MOSKOW: Yes, Your Honor. Thank you.

Q. Dr. Plunkett, in reaching your opinions in this case, did you have an understanding as to who the warning should go to here in West Virginia?

A. Yes.

Q. And who is that?

A. To the patient. So the Medication Guide becomes the most important document.

Q. Even with that statement, I want to ask you a few questions about the doctor's label. All right?

A. Sure.

Q. And in particular, I want to ask you about this warning and precaution that says risk of bleeding -- and I'm looking at Exhibit 5884 right now.

A. Uh-huh.

Q. Risk of bleeding. Pradaxa can cause serious and sometimes fatal bleeding. Promptly evaluate signs and symptoms of blood loss.

Do you recall that?

A. Yes.

Q. And you were asked whether it was a strong warning.

Do you recall your answer to that?

A. Yes. I said it was.

Q. Okay. And you were asked whether it was a serious warning.

Do you recall your answer to that?

A. Yes, I do. I said it was.

Q. I have a question for you. Is it a complete warning?

A. No, and that's my issue.

Q. Explain that to the jury.

A. So it is well known by scientists and physicians, based on

what I have seen in the medical literature for sure, that everyone knows that anticoagulants cause bleeding, can cause serious bleeding. And I think Attorney Jones even pointed that out.

So the issue is, when you're telling doctors something in a warning about the risk of bleeding can be serious and sometimes fatal or life-threatening, but you know how to prevent it, you know that there's information that allows you to identify people who may not be at such -- or may be at a great risk and you could actually prevent or minimize that risk, that is what is incomplete.

You're not telling the physician, oh, by the way, it's serious. But identifying your patient -- whether or not your patient has excessive exposure or too much dabigatran or whatever word you use, in other words, taking a blood sample to understand where they fit with their risk factors, that is the warning -- part of the warning that I think is missing.

Q. And that's even in the doctor's label?

A. That's correct.

Q. We're not even talking about the patient Medication Guide.

A. That's correct.

Q. Now, you testified that there were changes to the label over time; is that right?

A. Yes.

Q. I want to go back to Exhibit 86, if we could quickly. And

I want to look at Section 5.1 which has to do with the risk of bleeding.

A. Okay.

MR. MOSKOW: And hopefully everybody can see this, but we'll read along just so it's clear.

Q. This section on risk of bleeding doesn't specifically mention anything to do with renal concerns, does it?

A. No, not in this section.

Q. And if we go to the later label, Exhibit 5884, that January 2002 [sic] label, in Section 5.1 there on page 3, there is specific language about Pradaxa's anticoagulant activity and half-life are increased in patients with renal impairment.

Do you see that?

A. Yes.

Q. Can you tell the jury when Boehringer sent a dear doctor or dear health care professional letter out to U.S. doctors telling them that that change had been made in the warning section of the Pradaxa label?

A. I have not identified a letter where they did that.

Q. So is the simplest way you haven't seen a letter that went to doctors?

A. I have not seen a letter that went to doctors to tell them, and this is important information.

Q. With regard to adverse reactions and drug interactions --

I'm looking at Exhibit 86 on the highlights.
A. Okay.
Q. Is there any information there about dangerous drug interactions that a physician needs to be aware of?
A. Not in this highlights section, no.
Q. If we look at 5884, the January 2002 [sic] label, has there been information added about dangerous drug interactions?
A. No, not in that section. Although, to be fair, there is something in warnings and precautions up above, but not under adverse reactions.
Q. How about in drug interactions?
A. Oh, no. I'm sorry. Yes, that's correct, there is. Yes.
MR. MOSKOW: I know it's been a long day --
THE WITNESS: I'm sorry.
MR. MOSKOW: -- and I'm bouncing around.
And to be fair, you and I haven't been able to speak in 12 hours, so we haven't had a chance to talk about this.
THE WITNESS: Yeah, I thought you were looking up there under adverse reactions. I apologize.
BY MR. MOSKOW:
Q. But there is a specific warning now saying P-gp inducers, right?
A. Yes.
Q. And a specific warning saying P-gp inhibitors?

A. Yes, there is.
Q. And now there's a third warning that says P-gp inhibitors in patients with severe renal impairment, Pradaxa use is not recommended.
A. Yes.
Q. Is that important information?
A. Absolutely.
Q. Why is that important information?
A. Because that's the discussion I had about the fact that you put together severe renal impairment and put together P-gp inhibitors, and you don't know what level of drug is in the blood, those people are at much greater risk.
Q. Can you tell the jury when Boehringer sent a letter to doctors in the United States telling them that they had added this important information about significant drug interactions for people with really bad kidneys?
A. I have not seen a letter. I'm not aware of them having done that.
Q. Do you remember, Doctor, that you were shown a few moments ago Exhibits 5062 and 5036, which were marked-up labels during the negotiation between the FDA and Boehringer?
A. Yes.
Q. With regard to 5062, could I turn you to page 17 of the document?
A. Okay.

Q. And do you see that that is the Medication Guide?
A. Yes.
Q. Can you tell the jury whether there were any changes that the FDA recommended to the Medication Guide?
A. There is none.
Q. Well, I mean, they did some indenting of bullet points.
A. Well, I meant substantive changes.
Q. Okay. All right. Let's look at Exhibit 5036. Can you look at pages 22, 23, 24.

Are there any changes that the FDA recommended to that Medication Guide?
A. No.
Q. Have you seen any indication that BI proposed specific language regarding the drug never being tested in people with severe kidney problems, that the 75-milligram dose had never been tested, that people should not take Pradaxa and Coreg, that there was no reversal agent, and that you are more likely to have a GI bleed with Pradaxa than with warfarin?

Have you seen any evidence that any of those statements were proposed to be put in the Medication Guide?
A. No, I've not seen any indication that that was ever proposed.
Q. Doctor, you were shown many, many documents today including -- and yesterday including one of them Exhibit 5827, which was the summary review document.

Do you recall that?

A. Yes.

Q. And you were shown a lot of pages in here. You were shown, you know, who actually reviewed the document, and there was specific language that was called to your attention.

But in all the language you were shown, you weren't shown this part at the end, Risk Evaluation and Mitigation Strategy or REMS.

Do you see that?

A. Yes.

Q. And I specifically want to bring this paragraph to the jury's attention.

Could you read that slowly into the record, please, the one that I have highlighted on the screen?

A. Sure.

The review team has opined that a Medication Guide is required for dabigatran because dabigatran poses a serious and significant public health concern. The Medication Guide is necessary because, No. 1, patient labeling could help prevent serious adverse events; and, 2, there are serious risks that patients should be made aware of because information concerning the risks could affect patients' decisions to use or continue to use dabigatran.

Q. Do you agree with that statement?

A. Yes.

Q. Was that a statement that you had in your mind when you were reaching your opinions as to whether the Medication Guide was sufficient, was adequate for people to make an informed decision about whether to take Pradaxa?

A. Yes. The standard I was using when I reviewed it was looking at what FDA had said about the fact that the issue of preventing adverse events, that's an important one, prevent them before they occur. And then the other one about the fact that patients need to be aware so they can make an informed choice.

Q. Now, even though we've been talking about various labels, would you agree that if Boehringer wants to make that change in a label, there is a process that it can do that?

A. Yes.

Q. Okay. So, for example, we were looking at the January 2012 label that is Exhibit 5884.

Do you recall that?

A. Yes.

Q. And when we look at the Medication Guide there, and what you went over today with Attorney Jones, it looks like this, right?

A. Yes.

Q. All right. And when you and I were looking at the document yesterday, we looked at Exhibit 93, which was the April 2013 label.

Do you recall that?

A. Yes.

Q. And that label looked like this.

Do you see that?

A. Yes. The front part is a bit different.

MR. MOSKOW: I want to -- and usually I would do this on the screen with Gina helping me, but in the interest of time, I just want to see if we can do this kind of side by side here.

Q. Do you see in the 2012 label, the very first thing under what's the most important information I should know about is that Pradaxa can cause bleeding which can be serious and sometimes lead to death?

A. Yes.

Q. Can you tell the jury what the very first thing in the 2013 label is under what is the most important information I should know about Pradaxa?

A. It's actually telling you about how it works, not about the bleeding risk.

Q. Okay. And so Boehringer decided over time to change its Medication Guide and actually move down the importance of Pradaxa can cause bleeding which can be serious and sometimes lead to death?

A. That's correct.

Q. And is that consistent with the company's ability to make

changes to its labeling if it wants to?

A. Yes.

Q. Let's stick with the 2013 label, if we could.

Now one of the criticisms that you've told the jury about is that there is no information in the Medication Guide that indicates that the drug was not tested in AFib patients, right?

A. Yes.

Q. If you could turn to Exhibit 93, page 14.

Do you see at the very top of the page, there is information that says: It is not known if Pradaxa will harm your unborn baby?

A. Yes, I do.

Q. It says: It is not known if Pradaxa passes into your breast milk?

A. Yes.

Q. Do you know why that is?

A. It hasn't been tested.

Q. So if they want to put information in the label regarding the fact that it hadn't been tested, is there evidence that you've found that would show they're capable of doing that?

A. Yes, I believe they can.

Q. Finally, Doctor, I want to ask you about whether there is information in the label -- in the Medication Guide that you believe -- strike that.

Let me ask you whether there is information that you believe should be in the Medication Guide that is not.

A. Yes.

Q. And I want to start by showing the jury something they've seen before, which is something talking about the risks and benefits of Pradaxa.

Do you see that?

A. Yes.

Q. I don't know whether you've seen this before, but the jury has. And one of the things that this shows is that there are benefits to Pradaxa, right? The stroke risk, the life-threatening bleeds, and the haemorrhagic stroke is lowered?

A. Yes.

Q. But there is a risk in gastrointestinal bleeds, correct?

A. Yes. Higher, yes.

Q. Is that among the most important information that should be included in a Medication Guide?

A. I believe so because this was the ultimate conclusions of the outcomes of RE-LY. So, yeah, this is the study that was done, the most controlled and the largest study that they did. So yes, I do.

Q. Okay. And, in fact, if we just look really quickly at Exhibit 5884, on I believe the next to last page of the exhibit, page 14, Boehringer says that the Medication Guide

summarizes the most important information about Pradaxa.

Do you believe that the Medication Guide can summarize the most important information about Pradaxa if it doesn't include information on the important identified risk of increased gastrointestinal bleeding?

A. No, I do not. I think that's a very important -- was a major outcome from the trial.

Q. Doctor, I started my examination with you and I am going to end my examination today, to the extent that the Medication Guide does not include information about never having been tested in patients with severe kidney problems, that the 75-milligram dose was never tested, that people shouldn't take Pradaxa and Coreg, that there is no reversal agent, and that there is no information about the -- or I'm sorry -- and the issue of GI bleeding, have you formed an opinion as to whether the Medication Guide fairly, accurately and completely describes the most important information about Pradaxa to patients here in West Virginia?

A. I have.

Q. And what is that opinion?

A. That it does not. And these are the areas that I believe are missing, although I would make one small change, never tested in AFib patients with severe renal impairment.

Q. Fair enough.

And, Doctor, are all of the opinions that you've given

this afternoon, as well as everything that has happened during your examination, been to a reasonable degree of scientific and regulatory certainty?

A. Yes, they have been.

Q. And what does that mean to you?

A. That means it's more likely than not that my opinions are true.

MR. MOSKOW: Thank you very much, Doctor. That's all the questions I have for you.

THE COURT: Recross?

MS. JONES: Very limited, Your Honor.

RECROSS-EXAMINATION

BY MS. JONES:

Q. Dr. Plunkett, good afternoon again.

I have not brought my giant pile of paper with me, so I'm going to ask Mr. Reynolds to kind of help us see things on the screen. But if you need anything in hard copy that you don't have up there, let me know.

Okay?

A. Okay. Sure.

Q. I will be relatively brief.

You ended your discussion with Mr. Moskow by talking about the Medication Guide and what you think isn't in the Medication Guide and why it's inadequate, correct?

A. Yes. And why it's important as well to put those things

in, yes.

Q. Understood.

Would you agree with me that the Food and Drug Administration, over the course of time that Pradaxa has been on the market in the United States for atrial fibrillation patients, has approved that Medication Guide somewhere around 18 times?

A. I said I'm aware of at least a dozen, but I wouldn't argue with your number that they have done labeling changes, at least that many.

Q. Okay. Let me ask you a question about Exhibit 93 specifically.

Do you have that in front of you, Doctor?

A. I can, yes.

Q. Okay.

A. Yes, I'm there.

MS. JONES: Are we able to flip back to the third to last page or so, Mr. Reynolds, of the Medication Guide. I think it's page 11, page 10 or 11.

THE WITNESS: Page 12?

MS. JONES: Page 12, I was close. Okay.

Q. Now, again, this is the Medication Guide that was part of the labeling for Pradaxa from April of 2013, correct?

A. Yes.

Q. Okay. And one of the things that you just talked about

with Mr. Moskow was the fact that there is now additional information in that first section of the Medication Guide that is entitled What is the Most Important Information I Should Know About Pradaxa, correct?

A. Yes. And, actually, it's not so much additional. It's moved up. There was similar information before lower down.

Q. Okay. Do you understand that the way that is structured and that language was actually required by the FDA as part of a class labeling approach, and that you find that exact same language in the Medication Guide for Xarelto and for Eliquis, and it appears right at the top of that section?

Did you know that?

A. I am aware that there is similar language in the Xarelto. I haven't seen the Eliquis label, so I can't answer that.

Q. Okay. And did you know that that adjustment that you described in terms of the sequencing of things there and the information that appears there, that that was part of class labeling required by the FDA?

A. I haven't seen a document to confirm that, no.

Q. And you wouldn't -- you can't disagree with me because you've not looked into that specific question; is that right?

A. Yes. I've not seen documents to show that that is true, so --

Q. Okay. You talked some --

MS. JONES: We can take that down. Thank you,

Mr. Reynolds.

Q. You talked some about how someone might go about testing blood levels, correct?

You said, well, someone might get their kidney function checked, and you could just take some of that blood and use that blood to test blood levels, correct?

A. That's one of the ways you could do it, yes.

Q. That's what you said.

But you told us yesterday that you are not a medical doctor, correct?

A. I am not.

Q. You have no clinical experience, correct?

A. Not in treating patients, that is true. I've dealt with clinical samples before in the lab, but --

Q. You understand when I say treating -- when I say clinical experience, I meant in the context of talking about you not being a medical doctor.

What I mean is, you have not cared for patients during any part of your career, correct?

A. That is absolutely correct.

Q. And so some of the opinions that you've offered up about how someone might go about testing blood levels, those aren't based on any actual clinical experience that you've had caring for patients, correct?

A. No. It's based on knowledge, but not on my actual

clinical experience.

Q. You started your redirect examination with Mr. Moskow talking about what are known as PDUFA fees.

Do you remember that?

A. Yes.

Q. And that's something that not just Boehringer Ingelheim, but all medicine companies, pay as part of the review process, correct?

A. That is correct.

Q. And you're aware that those fees are paid to the FDA whether the medicine that is proposed is approved or whether it is not approved, correct?

A. That's true.

Q. And I was listening very carefully to both the questions and the answers that you gave.

You are not suggesting somehow that the company bought and paid for all of those doctors and scientists and professionals at the FDA who looked closely at the Pradaxa application, are you?

A. No, and I think I said that. There is not paychecks being written to the employees, which is I think what you're suggesting.

Q. And you're not suggesting that the company somehow bought the decisions or the analysis or the findings of the men and the women at the FDA who looked at the data submitted on

Pradaxa, are you?

A. No. I wasn't suggesting any -- anything untoward, which is I think what you're suggesting. I'm just stating that this is how the system works.

Q. Okay. I just wanted to clarify that.

And you understand that as part of the review process for Pradaxa, there was actually a panel of external doctors and scientists who looked at the application, something known as an advisory committee, correct?

A. Yes. I think you and I went over that the first day.

Q. I'm not sure that we did, but we're going to go over it now due to some of your testimony on redirect examination.

An advisory committee is a panel of experts convened by the FDA to provide independent advice, correct?

A. That is the goal, yes.

Q. And it's not -- it doesn't give binding advice to the FDA, but it votes on specific questions related to applications for prescription medicines, correct?

A. Yes, and your binding is correct. Sometimes they follow that advice, FDA, and sometimes they don't.

Q. In the case of Pradaxa, the question posed to the advisory committee generally was should this medicine be approved for patients who have atrial fibrillation, correct?

A. Yes, that's correct.

Q. And do you recall that the doctors and the scientists on

that advisory committee actually determined that the answer to that question should be yes?

MR. MOSKOW: Your Honor, could we go to side bar, please?

THE COURT: Yes.

(Bench conference, reported.)

MR. MOSKOW: Your Honor, I did not talk about the advisory committee. This is beyond the scope.

MS. JONES: Your Honor, the first questions he asked essentially suggested that the company had somehow bought off the decisions of the FDA. That's the only reason.

To ask did you know that the company had paid the FDA a million dollars for the review, he suggested that the --

THE COURT: So what is it you're trying to establish?

MS. JONES: That in addition to the FDA's review, there were external scientists who participated in the discussions surrounding the evaluation.

I'm not --

THE COURT: I will allow you one or two questions about that to establish there were others like these people --

MS. JONES: That's all I intend --

THE COURT: -- but to not get into the details or the substance of the report. I think that is beyond the scope.

MS. JONES: I don't intend to go much further on this.

THE COURT: All right.

(Bench conference, concluded.)

MR. MOSKOW: Your Honor, with the understanding of how the information is to be used, I withdraw the objection.

THE COURT: Okay. Why don't you restate your question or state a new one.

MS. JONES: I will do that, Your Honor.

Q. Dr. Plunkett, I think the last question I asked you before we went up to the bench was, is it your understanding based on your review of the materials that those independent doctors and scientists who looked at the Pradaxa application all voted unanimously that the medicine should be approved?

A. The medicine generally, yes.

Q. One of the things that you discussed with Mr. Moskow was this idea that there had been changes in the labeling for Pradaxa over the years.

You remember that?

A. Yes.

Q. And the doctor label, in particular, there were things that were added to the label over the life of the medicine.

Do you recall that?

A. Yeah. I don't think we did the whole life. We were in that period up to around 2013, yes.

Q. Right.

And just to be clear, that is not an uncommon thing that over time the label for a medication has changes to it,

correct?

A. No. Because often it's new indications that are sought, additional information.

Q. Okay. And in January -- by January of 2012, some of the information that we've been talking about, including that table that included information on patients with severe renal function and the fact that the RE-LY study hadn't tested a dose of the medicine in those patients, that was in the labeling for Pradaxa by January of 2012; is that right?

A. I can't confirm that it was January of 2012. I do know that it was -- that it was before 2013, but I can't tell you the exact month.

Q. Do you still have 5884 in front of you?

A. I can find it.

Q. Well, we can pull it up.

A. No, I've got it right here.

Q. And, again, just to situate ourselves, this is the first page of the labeling for Pradaxa.

And if you look down at the bottom part of the highlights section, you see that there is a reference to revised January of 2012?

A. Yes. Okay. So that is the January 2012, yes.

Q. Okay. And just to be clear because you were asked some questions, hypothetical questions about some of the issues in this case, you don't know one way or the other what Mrs.

Knight's doctors understood based on the labeling for Pradaxa, correct?

A. I have not had a conversation so, no, I can't speak to them specifically.

Q. Dr. Plunkett --

MS. JONES: We can take that down. Thank you, Mr. Reynolds.

Q. Dr. Plunkett, the last thing I wanted to ask you about was the questions that you covered on the clinical trial overview. Do you have 5084 in front of you?

A. I can get it. Yes, I do.

MR. MOSKOW: What exhibit number, counsel?

MS. JONES: 5084.

Q. Do you have that, Doctor?

A. Yes, I do.

Q. Okay. And I believe you were shown language on page 94 of 5084.

A. Yes, we looked at this.

Q. Okay.

MS. JONES: And if we can just call out that second paragraph, Mr. Reynolds, there may be subjects.

There may be subjects who have multiple risk factors for increased bleeding risk that together may substantially increase risk. And then it goes on to describe some of those, like concomitant antiplatelet use, concomitant P-gp inhibitor

use, age greater than 75, moderate renal dysfunction, previous bleeding, high CHADS scores, those factors that may increase bleeding risk.

THE WITNESS: Yes.

BY MS. JONES:

Q. Do you remember talking about that?

A. That's correct.

Q. Do you have an understanding that Boehringer Ingelheim actually tried to propose language very much like that for the U.S. labeling for doctors for Pradaxa, and the FDA rejected that language?

A. It's possible they did with the 110-dose issue, but I'm not -- but I'm not aware of it for the 75, the prescription of the 75.

Q. Well, you've raised a good point.

Because if we actually read down to the bottom of that paragraph, it says: While there may also be increased benefit in such subjects, the risk of bleeding may potentially outweigh the risk of stroke, and a dose of 110 milligram BID may be considered.

Did I read that correctly?

A. You did.

Q. And so that language was actually generated in the context of the discussion around whether or not there would be a 110-milligram dose of Pradaxa, correct?

A. Yes.
Q. Okay.
MS. JONES: Your Honor, may I approach, please?
THE COURT: Yes, you may.
MS. JONES: Dr. Plunkett, I've handed you what we've marked as 5054 and 5056.
Q. Have you seen those documents before?
A. I am not sure about the e-mail --
Q. Okay.
A. -- because I have a hard time with that sometimes. I don't usually see them attached.
Q. Okay.
A. I believe -- I believe I may have seen this presented to me before.
MS. JONES: Let me just ask my colleague one question.
(Defense counsel conferring.)
MS. JONES: Your Honor, we would move for the admission of 5054 and 5056.
MR. MOSKOW: No objection.
THE COURT: Each are admitted and may be published.
(DEFENDANT'S EXHIBITS 5054 and 5056 ADMITTED INTO EVIDENCE.)
MS. JONES: Dr. Plunkett, let's start with Exhibit 5054, if we could please.
And you can see just generally that this is an e-mail

exchange between Alison Blaus at the FDA and Michelle Kliewer at Boehringer Ingelheim concerning the application for Pradaxa in 2010.

Q. Do you see that?

A. Yes.

Q. Okay. And down at the bottom, you can see that there is an e-mail from Ms. Blaus where she has sent to Ms. Kliewer a copy of the non-clinical proposed labeling.

Do you see that?

A. Yes.

Q. Okay. And then if we move up towards the top, there is Ms. Kliewer's response saying: Hope you enjoyed the weekend. Please find attached our response to your proposed non-clinical label. We accepted the changes in Section 13. We have proposals for 8.1 and 8.2. I have attached the full proposed USPI that accepts some of the proposed changes and provides the CMC changes with a few format changes.

Did I read that correctly?

A. You did.

Q. Okay. And if we could, Doctor, let's go to 5056.

A. Okay.

Q. And we're going to go to page 9 of that document.

And just to orient ourselves, this is the -- 5056 is just the attachment that Ms. Kliewer provided in connection with her e-mail on September 27th, 2010, sending the proposed

non-clinical label.

On page 9, you see there's a section that refers to 8.7, High Risk Bleeding Patients?

A. Yes, I see that.

Q. Okay. And if we just pull -- thank you, Mr. Reynolds.

If we pull that language up, it says: For those patients with a potentially higher risk of bleeding, e.g. or for example, age over 75 years, CHADS2 score greater than three, moderate renal impairment, 30 to 50 milliliters creatinine clearance per minute, concomitant treatment with P-gp inhibitors or previous gastrointestinal bleed, a reduced dose of 110 milligram twice daily may be considered.

Do you see that?

A. I do.

Q. Okay. And do you understand that the FDA actually required the company to take that language out of the label in connection with its decision not to approve the 110-milligram dose of Pradaxa?

A. Yes. That was what the removal was linked to, the fact that it was linked to 110.

MS. JONES: We can take that down. Thank you, Mr. Reynolds.

Dr. Plunkett, I think I'm talking myself out of my voice, so I am going to stop, and thank you for your time.

THE COURT: All right. Anything else?

MR. MOSKOW: No, Your Honor.

THE COURT: All right.

MR. MOSKOW: We've had enough.

THE COURT: All right. Dr. Plunkett, thank you for your testimony. You can step down. We'll collect those later.

Ladies and Gentlemen, we already had a requirement that we adjourn for the day at 4:00, so there's no point in starting with any additional evidence. Obviously there's a lot more evidence for you to hear, so please keep these things in mind.

First, we will adjourn until Tuesday morning at 9:00. Monday is a federal holiday, and the courthouse is closed, so we will not have the opportunity to proceed Monday. So you're off. So we'll reconvene at 9:00 a.m. on Tuesday morning. We'll follow the same pattern next week as we have this week.

Please remember that the parties have put forth a huge amount of effort in this case, so don't violate my request or direction, rather, that you not investigate the case. Don't try to look anything up on your own. Don't try to talk to anybody about the case or let anyone discuss it with you.

I'm not going to tell you not to think about this case because that would be impossible, I'm sure. But please observe by letter and spirit the requirement that I've imposed upon you to keep an open mind.

With that, we'll see you back here on Tuesday morning.

Yes, sir.

JUROR NO. 15: Your Honor, with respect to us jurors who worked the day before and a half, do we get paid money?

THE COURT: No, afraid not.

JUROR NO. 15: Okay.

THE COURT: I invite you to write your congressman.

JUROR NO. 15: I asked all of the ladies that.

THE COURT: Ms. Justice is going to give you her phone number. Do all of you have your pads handy? Oh, she's already typed it up.

So I'm going to give you her phone number. If something happens, please let us know as soon as it happens if it's going to present any type of difficulty with you being back here on time on Tuesday morning. It's unusual that we go through a long weekend like this, so I want to make sure -- since it's three days, some things can change sometimes with people. If it does, please let her know immediately. She'll contact me, the parties and everyone.

So, with that, I'm going to ask everyone else to remain in the courtroom until all of the jurors have left. Go enjoy your weekend.

(Jury not present.)

THE COURT: You can be seated. I just want to take up a couple routine matters with you after the jury has left.

All right. First, I would point out it seems to me we're going pretty slow. I understand that that just may be necessary. But I want to remind everyone that I've given you the three-week period here to conduct this trial, and we're going to stick to that.

Generally I'm keeping somewhat track of how much time each side uses. I don't mean to single you out by any means, Ms. Jones. This is the first live witness we have had, so it's easy for me to bring this point to discussion based on that, but your examination on cross was as long or longer than the direct, which is fine. I will simply point out that I'm going to try to keep track and give the parties equal time.

So during this three-week period that we've got set aside, the plaintiffs will get no more than half of that time to present their case, and the defendant will receive no more than half of that time to present its defense.

MS. JONES: And, Your Honor, I will tell you, our experience is that Dr. Plunkett is always by far the longest witness. I frankly was moving at light speed with her compared to how things have gone in Connecticut. So I don't expect that we will have any witnesses who will run nearly as long as Dr. Plunkett.

THE COURT: Well, I appreciate that. I just wanted to make you aware that that is going to be my approach to it.

Also, I don't see any need for us yet to get into

final instructions, and I probably will wait until we're close to the end of the plaintiffs' case before I even start -- we've obviously got some drafting from the preliminary instructions, but I'm not going to even start to deal with that until we get pretty close to the end of the plaintiffs' case. But once we do, pretty soon after that, I'm likely to have the parties start communicating with each other and with the Court about final instructions.

And we'll discuss the different approaches that are options for how we get into that and have a fair, open discussion and preserve the record adequately for everyone, but I don't intend to get into that until we see the end in sight for the plaintiffs' case.

Is there anything else that you all know we need to address?

MR. CHILDERS: Not that I'm aware of, Your Honor.

MR. LEWIS: We've got one minor issue that I just wanted the Court's guidance on, if I could, Your Honor.

THE COURT: Okay.

MR. LEWIS: Based on the testimony of Dr. Plunkett, we're anticipating on our side a pretty significant legal issue at the directed verdict stage on warning preemption under federal law. And we're -- it's not the kind of motion that you make just on your feet in real time like a lot of directed verdict motions are. So we thought we would get the

Court's guidance on should we be throwing some papers in maybe a little bit early on the scope of the law and things along those lines for Your Honor's benefit.

THE COURT: Well, the easy answer to that is, yes, the sooner the better.

If you believe, given your understanding of the balance of the plaintiffs' case in chief, that the testimony of Dr. Plunkett and the other testimony that is heard will set the stage for the Court's practical consideration, then the sooner the better is all I can say.

MR. LEWIS: Fair enough. Thank you, Your Honor. Appreciate that.

THE COURT: Okay. The last thing I'll note again -- I know you folks are staging from different places here.

The courtroom will be locked and secured through the weekend. So if you feel like it's easier to leave things here, feel free to do that. I think it will be safe. We've never had any problems. So if that helps, makes it a little easier than moving all of this stuff out and then having to come back here early on Tuesday morning to reassemble it, that is certainly your option.

We'll have the courtroom reopened by 8:30 on Tuesday. So until then, it will be locked when we end today. We won't lock up until we know you all are ready this evening or this afternoon.

All right. Is there anything else? If not, see you back here Tuesday. Have a good weekend.

MR. MOSKOW: Have a good weekend, Your Honor.

MR. LEWIS: Thank you, Your Honor.

MR. CHILDERS: Thank you, Your Honor.

THE COURT SECURITY OFFICER: All rise. This honorable court will be in recess.

(Proceedings were adjourned at 3:56 p.m.)

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CERTIFICATION:

We, Kathy L. Swinhart, CSR, and Lisa A. Cook, RPR-RMR-CRR-FCRR, certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter as reported on October 5, 2018.

October 6, 2018
DATE

/s/ Kathy L. Swinhart
KATHY L. SWINHART, CSR

/s/ Lisa A. Cook
LISA A. COOK, RPR-RMR-CRR-FCRR